Explaining Natural Variability in Human Memory with Genes and Brain Structure

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Abbreviations:

ADCY8 – Adenylyl cyclase 8
ADT – Androgen Deprivation Therapy
AMPA – Alpha-3-hydroxy-5-methyl-4- isoxazolepropionic acid
AVLT – Auditory Verbal Learning Task
BDNF – Brain-derived neutrophic factor
BPVS – British Picture Vocabulary Scale
CA – Cornu Ammonis
CamKII – Ca2+/calmodulin dependent protein kinase
cAMP – Cyclic adenosine monophosphate
CREB – cAMP response element binding
EC – Entorhinal cortex
ERK – Extracellular signal regulated kinase
FD – Fimbria dentate
fMRI – Functional magnetic resonance imaging
HATA – Hippocampal-amygdaloid transition area
LTP – Long-term potentiation
MAPK – Mitogen-activated protein (MAP) kinase
MCI – Mild cognitive impairment
Met – Methionine
MRI – Magnetic resonance imaging
NMDA – N-methyl-D-aspartic acid
PCR – Polymerase chain reaction
PKA – Protein kinase A
PKC – Protein kinase C
PKCζ – Protein kinase Mζ
PRMQ – Prospective and Retrospective Memory Questionnaire
RFLP – Restriction fragment length polymorphism
RT – PCR – Reverse transcription polymerase chain reaction
SNP – Single nucleotide polymorphism
SUB – Subicular Cortex
T-RFLP – Terminal restriction fragment length polymorphism
Val – Valine
VBM – Voxel-based morphometry
WMS – Wechsler Memory Scale

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Abstract

The aim of this study was to investigate the influence of candidate genes and brain structure on memory performance. A foreign word-pair association paradigm was designed to provide several dissociable measures of different memory processes. Subjects deeply encoded foreign word pairs with a picture-word matching task. They were tested at five time points over one week which provided measures of learning and forgetting rates, dissociable between measures. Performance was evaluated with respect to the genotype of three candidate genes; brain volume of memory-related structures evaluated by VBM; and metamemory assessments from a questionnaire. The expected trends of influence of these genes on specific memory processes were observed but failed to reach significance. Temporal influences were not dissociable between genes as hypothesized. We attribute our overall lack of significant correlations to such few participants. Significant findings were found by VBM between parahippocampal gyrus volume, BDNF genotype, and working memory performance. Despite the lack of many significant findings, the consistent trends between genotype, metamemory, and memory performance indicate worthwhile directions of investigation. Moreover, explaining variability in memory performance proved to be accessible through genotypic and VBM analysis.

1.1 General Introduction

Understanding how memory and learning function is not only an interesting biological question, but an epistemological one as well. How we live, act and create ourselves in the present is influenced by how we incorporate our past. Individuals vary widely in terms of what they remember and what they forget. The scientific study of memory is concerned with the neurobiological underpinnings of this variation. There are many angles from which to approach this study but as memory is a heritable trait, studying it via genetics is a viable route (McClearn *et al.* 1997). Identifying genes that confer better or worse memory function can provide insight into the molecular foundations of memory and can also indicate which neuroanatomical regions are critical. Practically, the identification of significant genes and how they affect particular aspects of memory could be used to design optimal strategies for learning that would be appropriate for individuals with particular genotypes.

Putatively significant genes for memory can be identified from genome wide scanning in conjunction with a behavioural paradigm. They may also be found by studying the molecular underpinnings of memory and exploring the genes involved in key parts of these pathways. Once a gene is associated with memory function, it is not sufficient to simply say a particular gene is relevant. In order for the discovery to be meaningful, the role of these genes must be fully characterized. This involves outlining the time course of activity and the specific memory processes for which it is critical. Memory formation and decay follow several stages (encoding, consolidation, storage, retrieval), all of which follow a timeline and have different cellular and neural correlates (Abel & Lattal 2001). We identified a cluster of potentially critical genes from genetic association studies. Subsequently, we delved into the molecular correlates of these genes in relation to memory processes in order to design a paradigm that would allow

the clearest characterization and dissociation of the roles of these genes. Ultimately, we formed hypotheses about 3 candidate genes concerning when and which kinds of memory processes they would influence.

1.2 Characterizing Memory Genes: Molecular Underpinnings - Memory by Time Course

Timing is central to the study of memory. Because memory phases are distinguished by their time course behaviourally and molecularly, it follows that genetic influence will have a defined temporal profile. However, it must be noted that the molecular processes underlying memory have not been completely elucidated. Long-term potentiation (LTP) is the molecular model for memory formation so the molecular cascades upon which LTP is founded are presumed to underlie behavioural memory processes (Matynia, Kushner & Silva 2002). There is evidence that parallel and somewhat independent molecular signaling cascades underlie different temporal phases of memory (Izquierdo *et al.* 2006). The division between these different phases is commonly based on whether they are protein-synthesis independent or dependent, but alternative views exist as to how and if this basis for the division is justified (Routtenberg 2008). These views assert that protein synthesis may not be the divisive mechanism underlying long-term memory (Routtenberg 2008). Proponents of these alternative views maintain their opposition because of methodological shortcomings of the experiments which supposedly support the protein-synthesis dependence view (Rudy 2008). Nevertheless, there is strong evidence that supports a dual-process theory (Abraham & Williams 2008).

Despite the fact that the cellular underpinnings of memory have yet to be settled, the reality remains that there is a sequence of molecular events that occurs after training. Furthermore, whether or not these molecular cascades fuel protein-synthesis or post-

translational modification, many of the kinases in these cascades have distinct temporal profiles of activity (Izquierdo *et al.* 2006). Short-term memory is considered protein synthesis independent while long-term memory is dependent, and intermediate-term memory is a mechanistic blend of the two (Stough, Shobe & Carew 2006). These phases can be dissociated from each other (Stough, Shobe & Carew 2006) through pharmacological treatments which disrupt or enhance one phase of memory while leaving a later one intact (Izquierdo *et al.* 2002). Stough *et al.* compared the molecular cascades that occur in short-, intermediate-, and long-term memory using sensitization in aplysia, and associative olfactory learning in drosophila and apis. They identified PKA, MAPK, and PKC to be crucial for transcription independent phases of memory formation, and they all require some PKM activity during the intermediate phase of memory. Phases dependent on PKA and MAPK require translation whereas those dependent on PKC do not (Stough, Shobe & Carew 2006). Evidently, multiple and separate molecular cascades are activated at different times during the process of memory consolidation.

Izquierdo *et al.* compiled the pharmacological evidence for systems-level consolidation in rats (2006). Consolidation, whereby memories become stable over time, is commonly thought to comprise of a rapid process (synaptic consolidation) and a much slower process (systems-level consolidation) that can last up to days or years (Medina, Bekinschetin, Cammarota & Izquierdo 2008). Subsequent to encoding, they tracked the peak activations of various molecules in CA1 over time. AMPA, metabotropic, and NMDA glutamate receptors are all activated, which leads to increased intracellular calcium concentration and consequently, activation of CamKII by 1 hour after encoding (Izquierdo *et al.* 2006). Many kinases are activated soon thereafter, provoking further molecular events. Figure 1 illustrates when certain

molecules are the most sensitive to inhibitors (Izquierdo *et al.* 2006). Of importance to our study, they found cAMP and PKA to have two peaks during consolidation: immediately, and the larger occurring 3 hours after encoding. PKC peaks at roughly 30 minutes after encoding

Temporal Activity of Molecules after Encoding (Izquierdo *et al.* 2006)

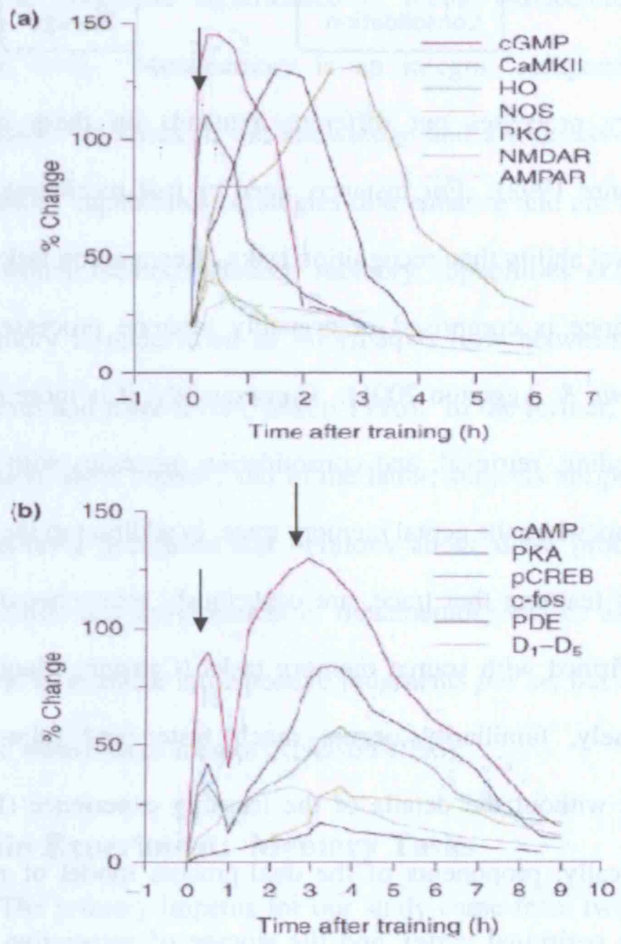


Figure 1

1.3 Characterizing Memory Genes:

Psychological Manifestations - Memory by Information Type

Because memory is not a monolithic faculty, but rather a complex conglomerate of processes, memory studies use a plethora of different tasks in order to observe them. As these different kinds of memory have unique temporal patterns as well as different

molecular and neural correlates, it is important to test all of these different facets of memory ability in order to clearly investigate the role of our candidate genes. Hence we designed our paradigm to not only measure memory decline over time, but to provide measures of several kinds of memory.

Memory formation involves several mechanisms that all have neural correlates:

Different memory processes put different demands on these mechanisms (Haist, Shimamura &Squire 1992). For instance, cued or free recall tasks provide a clearer measure of retrieval ability than recognition tasks. Recognition tasks are more complex because performance is comprised of arguably separate processes: familiarity and recollection (Brown & Aggleton 2001). Consequently, it is more difficult to separate demands on encoding, retrieval, and consolidation processes with a recognition task. Recollection occurs when the actual memory trace, in addition to the rich recollection of the experience of learning that trace, are consciously remembered (Yonelinas 2002). This can be confirmed with source memory tasks (Cansino, Maquet, Dolan & Rugg 2002). Conversely, familiarity occurs much faster and relies on a feeling of remembering but without the details of the learning experience (Brown & Aggleton 2001). Anatomically, proponents of the dual-process model of recognition localize familiarity to the perirhinal cortex and the storage of associative information to the hippocampus, which is crucial for the contextual nature of recollection (Brown & Aggelton 2001). Several other tasks of explicit memory can concurrently corroborate and tease apart contributions of encoding or retrieval to overall memory performance. These include working memory tasks, which tax attention capabilities (Baddeley 1998); spatial memory tasks, which can provide measures of episodic and source memory (Burgess, Maguire & O'Keefe 2002); and pattern separation tasks, which require

separating overlapping and similar memories into separate representations (Bakker, Kirwan, Miller & Stark 2008). These tasks also have neural correlates. Working memory involves fronto-parietal-cerebellar regions; and spatial, order memory and pattern separation tasks each implicate different structures of the hippocampus (Kesner, Gilbert & Wallenstein 2000).

The pragmatic significance of memory-associated genes is evident at the cognitive level. Metamemory is an integral component of memory ability and performance. It refers to the knowledge and awareness individuals have about their own memory capabilities, strategies that enhance and are appropriate to specific tasks, and of which factors influence memory capabilities (Larkin 2007). Conceptually, metamemory is understood as information flow between two levels of organization, object-level and meta-level (Nelson 1996). In the former, subjects encode and retrieve information about objects, and in the latter, subjects are probed about their knowledge of object-level processes and opinions about these processes (Nelson 1996). The sophistication and development of metamemory can be assessed experimentally. The aim is not to evaluate introspective judgments *per se*, but rather to relate them to other empirical measures of memory (Nelson 1996).

1.4 Main Experiment: Memory Tasks

The primary impetus for our study came from two genetic association studies. The first study found the Kibra intronic SNP rs17070145 to be associated with memory performance in three independent cohorts on a verbal free recall task when tested at 5 minutes and 24 hours. Subsequently, they associated the gene with differential hippocampal activation during a face-profession association task evaluated by fMRI (Papassotiropoulos *et al.* 2006). Through RT-PCR, immunocytochemistry, and Western blotting, they found Kibra to be expressed in memory-related structures in human brain,

including the hippocampus. In situ hybridization in mice showed the highest expression of Kibra in the dentate gyrus and CA1 (Papassotiropoulos *et al.* 2006). Almedia *et al.* replicated the finding that the T allele confers better performance on episodic memory in older, healthy individuals, but that it had no influence on risk of developing Mild Cognitive Impairment (MCI) (Almeida 2007). Kibra is identified as a selective and specific substrate of PKCζ, an atypical isoform of PKC that is clearly implicated in molecular memory cascades. Persistent phosphorylation by PKCζ is required in the maintenance of long-term potentiation and memory (Buther *et al.* 2006). When PKCζ activity was inhibited at various times after tetanisation of the Schaffer collateral/commissural-CA1 synapses, established LTP was reversed specifically at only late stages of LTP (Serrano, Yao, & Sacktor 2005). More recently, inhibition of PKCζ in rat insular cortex reversed established long-term memory associations and lasted for several subsequent weeks, indicating that PKCζ activity is necessary for long-term memory storage (Shema, Sacktor & Dudai 2007). Furthermore, inhibition initiated many days after learning could still extinguish memory, indicating that perhaps cellular/synaptic consolidation lasts much longer than expected, or that persistent kinase activity is required for memory maintenance indefinitely (Shema, Sacktor & Dudai 2007).

The second study investigated a cluster of genes associated with differential performance on a verbal memory task and found ADCY8 SNP rs263249 to have the strongest association of the cluster (De Quervain & Papassotiropoulos 2006). ADCY8 is directly activated by calcium and is involved in PKA, ERK, and CREB signaling but much less is known about its relationship with memory performance (Zhang *et al.* 2008). Zhang *et al.* found that ADCY8 was associated with spatial reference memory in a knockout study with rats. Because PKA activity peaks twice after encoding and is

necessary for memory formation (Izquierdo *et al.* 2006), presumably ADCY8's influence on memory performance is exerted in earlier rather than later stages of memory.

The final set of studies that shaped our study concern BDNF and its role in the persistence of long-term memory. BDNF has long been associated with neuronal growth and synaptic plasticity, and consequently its role in memory is of great interest (Bekinschtein *et al.* 2007). Over 100 studies published recently have investigated this phenomenon. Work from Bekinschtein *et al.* sought to define the temporal and mechanistic influence of BDNF in memory. Using an inhibitory avoidance paradigm in rodents, they disrupted BDNF function at various time points, and discovered that BDNF activity via an ERK-dependent mechanism was necessary and sufficient for long-term memory persistence specifically at 12 hours after training (Bekinschtein, Cammarota, Izquierdo, & Medina 2008). They postulate that BDNF's activity may account for why certain long-term memories persist while others are forgotten (Bekinschtein , Cammarota, Izquierdo, & Medina 2008). Regarding human behaviour, a single nucleotide polymorphism at nucleotide 196 (G/A) causes Val/Met amino acid substitution at codon 66 implicated in episodic memory (Egan *et al.* 2003). On the Wechsler Memory Scale, revised version (WMS-R), Val carriers had significantly worse performance and showed lower hippocampal activity during memory processing (Egan *et al.* 2003). Bueller *et al.* showed that Met carriers had 11% reduced hippocampal volume as compared with Val homozygotes, suggesting that BDNF's could influence memory performance by directing changes in brain structure (Bueller *et al.* 2006).

The above genetic association studies established the importance of Kibra, ADCY8, and BDNF for memory formation, but exactly how and when these genes

influence memory remains unclear. It is reasonable to hypothesize that their biological mechanism of influence is related to the roles with which these molecules have respectively been associated: Kibra interacts with PKCζ, and ADCY8 lies upstream of PKA. We designed a paradigm that attempts to flesh out these details. Specifically, we decided to test subjects at 5 time points after encoding such that we could construct forgetting curves. From studies of the molecular time course of memory, notably Izquierdo *et al.*, we formed four hypotheses to test:

1) We hypothesized that both Kibra and ADCY8 would be associated with better or worse memory performance, but that their time courses would differ based on the molecular time courses underlying memory.
2) Kibra would be associated with memory performance at longer time scales because of its interaction with PKCζ whereas ADYC8 would be associated with memory performance at shorter time scales because of the early significance of PKA in memory formation.
3) We predicted that BDNF Val carriers will have worse memory performance however we did not form a specific hypothesis about when in time it would influence memory.
4) As one of the ways genes may causally affect behaviour is through their shaping of brain structure, we decided to conduct VBM analysis both with memory-related regions and BDNF. Because BDNF Met alleles have been associated with reduced brain volume in memory related areas (Pezawas *et al.* 2004, Bueller *et al.* 2006), we hypothesized that Met carriers would have smaller volume in memory related areas, and that this finding might explain the dissociation in behaviour we predicted.

Genes may impact memory directly or indirectly. An association between a polymorphism and brain volume indicates a possible route by which genes indirectly influence memory behaviour. Our paradigm involves measures of recall and recognition to assess retrieval, encoding, and general memory ability. We also included tests of working memory, source memory, spatial memory, order memory, metamemory and pattern separation to support the results of the main measures. Not only might our candidate genes influence performance on these measures differently, but because these measures implicate different brain areas, differential performance might also indicate how these genes relate to specific brain structures.

One caveat to this experiment is that genetic association studies require significantly large numbers of subjects (N= 100+) in order to produce strong results, negative or positive. Our study has only 18 subjects due to time constraints of the project. Hence results are unlikely to be significant; trends must be taken of indicative of effects. However, it is such trends that direct further large scale association studies.

2.1 Pilot Study: Introduction

We conducted a pilot study in order to justify our rationale for the main experiment. We varied several parameters to maximize certain measures that would be the most informative for the main study. Specifically, we tested several methods of both encoding and retrieval in order to see which would cause subjects to retain learned information the best, which would induce the best performance at retrieval, and which provide us with the cleanest pattern of decline over time. This is because for our main experiment, we firstly required the most robust method of encoding without ceiling or floor effects at retrieval. Secondly, we required the simplest pattern of decline over time so as to interpret any influence of our candidate genes as directly as possible. We hypothesized that shallow encoding would result in less retention than deep encoding,

but we were not sure which of our two deep encoding tasks would lead to the best retention of word pairs.

2.2 Materials & Methods

We tested seven subjects, all students in London, UK, and between the ages of 21 and 27. Subjects engaged in an encoding task where they viewed 144 Swahili-English word pairs. We used a foreign word-English word association design for several reasons. The Papassotiropoulos *et al.* group used a paired association design in their scanning study, and both of their genetic association studies used verbal tasks. Furthermore, learning foreign words is common activity; not only did we want to use it to tease out the effects of our candidate genes, but more generally we hoped to discover more about how people learn and forget foreign words. We chose Swahili words because it is a language not likely to be spoken by Europeans, it is not related to the Romance languages, and it is written in the alphabet (see Appendix; Nelson & Dunlosky 1994).

The pairs were divided into thirds and encoded each with a different method. In the first set, single Swahili-English word pairs appeared centred on the screen and subjects were told to study the words as best they could. In the second set, 4 different pictures were presented on the screen. The English word of the pair was displayed in the centre while the same Swahili word was displayed underneath each of the 4 pictures. Subjects had to indicate which picture correctly corresponded to the English-Swahili word pair displayed. In the final set, the Swahili-English word pair was presented at the top of the screen. 4 English sentences were typed below the pair, each with the Swahili word embedded somewhere in the sentence, replacing the appropriate English word of the pair. Subjects had to indicate which sentence was appropriate to the Swahili-English word pair presented. In sum, subjects encoded one third of the words shallowly

and two thirds deeply. The pictures were taken from the British Picture Vocabulary Scale (Figure 2, BPVS). The word pairs came from Nelson and Dunlosky's Swahili-English word pair norms, combined with the word list from the BPVS which we translated into Swahili using the online Kamusi Project (http://kamusiproject.org/) in order to have enough pairs. We constructed the sentences ourselves. All stimuli were presented using Cogent (www.fil.ion.ucl.ac.uk).

Encoding Stimuli: English-Swahili Picture Matching Task

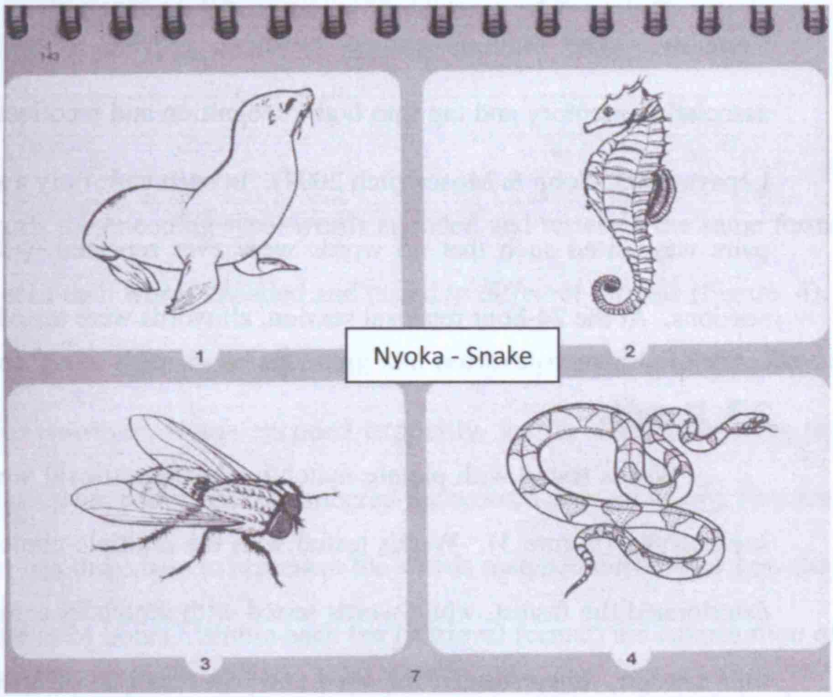


Figure 2

Subjects were tested during three retrieval sessions: 1 hour, 3 hours, and 24 hours after encoding. After encoding and in between the first and second retrieval sessions, subjects performed verbal intelligence and digit span tests in order to prevent rehearsal. At retrieval, subjects were first given a cued recall test where the Swahili word was presented on the screen and subjects were required to type in the English and they were encouraged to guess in cases of uncertainty. Subjects had to make a

Remember/Know/Guess judgment about their responses. Next they performed picture matching and subsequently sentence matching tasks, where the Swahili word was presented on the screen and they indicated which of the 4 options was a correct match. Finally, subjects were given a multiple choice style of test (Achim & Lepage 2005) where a Swahili-English word pair was presented and 5 possible choices were given beneath: i) Correct Translation ii) Incorrectly matched iii) Swahili word is familiar iv) English word is familiar v) Never seen either word before. After indicating their choice, subjects made certainty judgments ranging from 1) Guessing, to 4) Complete Certainty. The multiple choice questions provide a measure of both item and association memory and tap into both recognition and recollection processes (Achim & Lepage 2005, Cohn & Moscovitch 2007). In each task, only a subset of the original 144 pairs was tested such that no words were ever repeated within or between retrieval sessions. At the 24-hour retrieval session, all words were tested.

2.3 Results

Words tested with picture matching during retrieval were remembered the most successfully (Figure 3). Words tested with the multiple choice intact/rearranged pairs deteriorated the fastest, while words tested with sentences actually improved at the last time session. Interestingly, the cued and free recall tasks demonstrate a different time course than the three recognition tasks. Subjects perform better at 24 hours than in the immediate retrieval sessions for recall. We speculate that the consolidation induced by sleep affects recollection differently than it does recognition memory.

Overall Pilot Retrieval Results

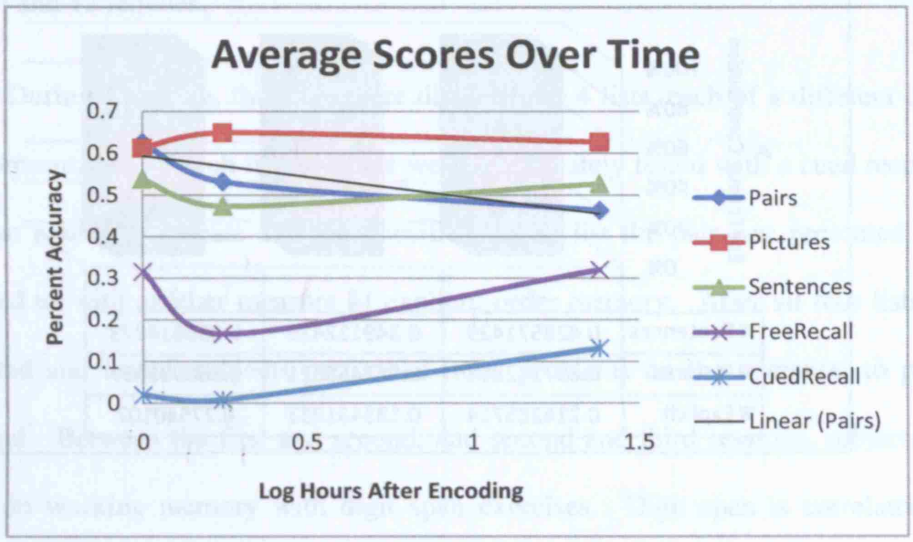
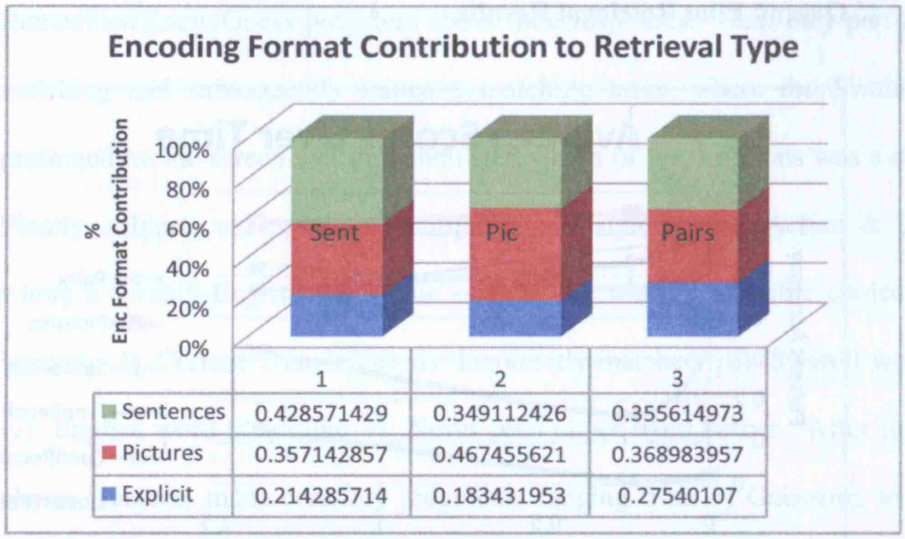


Figure 3

As regards the encoding type, words encoded and tested in the same format are better remembered than words encoded and tested in different formats (Figure 4). This is not surprising given theories of encoding and retrieval matching (Kahn, Davachi & Wagner 2004). However, words encoded explicitly, that is with instructions to learn words without deep encoding, are remembered the worst across all testing formats. The following chart has three bars to represent the words matched correctly across the three retrieval formats at 24 hours. Within each bar (retrieval format) the contribution of each encoding type to words correctly matched in that retrieval format is displayed. Comparing each encoding method contribution for a given retrieval format, all comparisons were significantly different from each other except when words were tested by sentences. Although there is a trend for words encoded with sentences being better remembered, it is not significantly better than words encoded with pictures ($p=.106$). The deep encoding tasks (encoding by either sentence or picture matching) contribute most to successful word retrieval.



	1	2	3
Sentences	0.428571429	0.349112426	0.355614973
Pictures	0.357142857	0.467455621	0.368983957
Explicit	0.214285714	0.183431953	0.27540107

Figure 4

2.4 Conclusion

In sum, deep encoding ensures words are remembered better than words encoded shallowly. We decided to use picture-matching instead of sentence-matching as our deep encoding task for the main study because the stimuli were easier to control and because we generated the sentences ourselves, which were therefore not standardized for difficulty, complexity, or length. In contrast, the pictures came from a standardized test. Concerning retrieval, we decided to use the pairs as our method for the main study. Words tested by this method followed the simplest pattern of decline over time compared with other retrieval methods which was precisely what we required for our main experiment.

3.1 Main Experiment: Materials & Methods

Analysis of our pilot data indicated that words encoded and tested by pictures were best remembered. Although words tested and learnt with sentences were nearly as robust, we rejected that method for the main experiment because the results from recognition memory did not provide the simplest decline over time. In fact,

performance improved slightly for words tested with sentences. We tested 18 subjects, 6 males and 12 females.

During encoding, the pairs were divided into 4 lists, each of a different colour. After presentation of each list, subjects were immediately tested with a cued recall task and also asked to indicate at which position in the list the pair was presented. This provided us with another measure of explicit, order memory. After all four lists were presented and tested, subjects performed math problems on the computer to prevent rehearsal. Between the first and second, and second and third sessions, subjects were tested on working memory with digit span exercises. Digit span is correlated with memory performance (recognition, recall, and others) and hence provided another measure that could dissociate between our genotypes.

Subjects were tested at 4 subsequent time points: 1.5 hr, 3 hr, 24 hr, and 1 week after encoding. The retrieval sessions consisted of cued recall and the 40 multiple choice style questions as outlined above. For those multiple choice questions with the correct answer being option i, iii, or iv, (the same options explained in the pilot section) subjects were subsequently asked to indicate in which colour each pair was presented (pairs was presented in 4 different colours on the screen) so providing a measure of source memory. We required subjects to make a certainty rating about their answers in a recognition memory task retrospectively. This kind of task concerns monitoring (in contrast to control) in metamemory (Pannu & Kaszniak 2005).

In contrast to the pilot study, we added a component at retrieval where the same subset of 48 pairs was encoded and tested with cued recall at each session. We decided to use repeated words as a measure of cued recall because in our pilot, subjects performed poorly on cued recall for words studied only once. These repeated words provide a measure of learning rates and a contrast to the deterioration in memory of

non-repeated words. In the final session, all of the words were tested. Subjects also performed two new tasks. The first was a spatial memory task where subjects were presented with a picture-Swahili pair and were required to indicate in which quadrant the picture was presented during encoding – another source memory task. The second was a pattern separation task with modified words. An English word was presented with 4 possible options below. One was the correct Swahili translation, but the other 3 words were very similar to the correct Swahili word, with only one or two letters changed.

At the 24 hour session, subjects perform 4 runs in the fMRI scanner (however the data from the fMRI task are not included here). In the first two runs, subjects performed a picture-matching retrieval task. They were presented with a picture centered on the screen with a Swahili word underneath and were asked to indicate if the pair was i) Intact ii) Rearranged iii) Novel or iv) a Guess. We encouraged subjects to avoid option iv if possible. In the third run, subjects encoded a new set of 40 word pairs taken from the Nelson & Dunlosky list (see appendix). No pictures were used; pairs were encoded explicitly. With each pair, subjects were required to make a judgment of learning whereby they indicated on a scale of 1 to 4 how difficult or easy they thought the pair was to learn. In the fourth run, they were tested on a subset of the word pairs learnt in the third run. A word pair was presented on the screen and subjects had to indicated if the pair was i) Intact ii) Rearranged iii) Novel or iv) a Guess.

At the final session, we gave subjects a pen and paper questionnaire to complete. The questionnaire asked information about sleeping habits, alcohol and drug use, and had two metacognitive questions. These asked subjects to rate themselves on a scale of one to ten (worst to best), as compared to others, first on their memory ability, and second on their ability to learn other languages.

3.1.2 Genotpying

We genotyped our 18 subjects for ADCY8 (rs263249), Kibra (rs17070145), and BDNF (val66met) with RFLPs. Additionally, we genotyped 282 subjects for BDNF in order to conduct a VBM analysis of their MRI structural brain images. The primers for all three genes were designed on Primer3 (http://frodo.wi.mit.edu/) using information from HapMap (http://www.hapmap.org/):

- Kibra: forward primer-TTTACTCCCAGCACACACCTC, reverse primer-CCACAGCCTTGTTCATTGTG;
- ADCY8: forward primer- TGATCTTAGGCTAGTTACTCCCTTTAC, reverse primer- TGAGCCTCAGTGACCTCCTA;
- BDNF: forward primer-CTCTGGAGAGCGTGAATG, reverse primer-ATACTGTCACACACGCTCAG.

The PCR reaction was blasted with the UCSC electronic PCR tool. Enzymes were chosen with Nebcutter (http://tools.neb.com/NEBcutter2/index.php) and obtained from New England Biolabs and the Taq polymerase was ordered from Molzym. Kibra was genotyped with a standard RFLP protocol while ADCY8 and BDNF were genotyped with T-RFLP (terminal restriction fragment length polymorphism, whereby one primer is fluorescently labelled so as to be precisely sized with a DNA analyzer).

We performed two optimizations for ADCY8 and Kibra with touchdown PCR. The first was for the reaction mix and the second for the annealing temperature. After optimization, the PCR reaction mixes and conditions for the three genes were as follows:

Table 1 – PCR Mixes

PCR	Buffer	Mg++	ForPrimer	RevPrime	Taq Polym	dNTP	DNA	Water	Total Volume
Kibra	10 µl	3 µl	.25 µl	.25 µl	.25 µl	1 µl	2 µl	33.75 µl	50 µl
ADCY8	2.5 µl	1 µl	.5 µl	.5 µl	.125 µl	.5 µl	1 µl	18.88 µl	25 µl
BDNF	1.25 µl	.5 µl	.25 µl	.25 µl	.0625 µl	.5 µl	.5 µl	9.19 µl	12.5 µl

Table 2 – PCR Conditions

PCR								
Conditions	Kibra	95°C	94 °C	59 °C	72 °C	Cycles	72 °C	4 °C
		5 min	.5 min	.5 min	2 min	35	7 min	∞
	ADCY8	95°C	94 °C	59 °C	72 °C	Cycles	72 °C	4 °C
		5 min	.5 min	.5 min	2 min	35	7 min	∞
	BDNF	94 °C	55 °C	72 °C	Cycles	72 °C	4 °C	
		.5 min	.5 min	.5 min	40	7 min	∞	

PCR and restriction digest with MnlI was performed for Kibra. The product was run on a 2.5% agarose gel at 80 volts for approximately 40 minutes. ADCY8 and BDNF were amplified with PCR with their forward primers fluorescently labelled with Hex and Fam, respectively. They were digested with HpyCH4IV and NlaIII, respectively. All digestions took place at 37 °C overnight.

Table 3 – Restriction Digest Mixes

Restriction Digest	Enzyme	Enzyme	NE Buffer	BSA	PCR Produc	Water	Total Volume
Kibra	MnlI	.5 µl	1.5 µl	.15 µl	5 µl	7.85 µl	15 µl
ADCY8	HpyCH4IV	.1 µl	1.5 µl	0 µl	5 µl	8.4 µl	15 µl
BDNF	NlaII	.05 µl	.5 µl	.05 µl	1 µl	3.4 µl	5 µl

After digestion, a solution concentrated with 3 µl of ladder per 1 µl of formamide was added to each well of ADCY8 and BDNF. The samples were then warmed to 95 °C for 5 minutes and immediately flash frozen on ice for 5 minutes. They were sized with capillary electrophoresis with the 96-capillary 3730xl DNA Analyzer. DNA fragment analysis was performed on GeneMapper v3.7 using the microsatellite default setting and the LIZ-500 ladder. Genotype frequencies for BDNF (n=286) were in Hardy-Weinberg equilibrium.

3.1.3 Voxel-Based Morphometry Analysis

The 206 images for the VBM analysis were obtained from both the 1.5T Siemens Sonata scanner and a 3T Siemens Allegra scanner at the FIL (London, UK). The images were acquired using a 3D MDEFT sequence (Deichmann 2000). VBM analysis was performed with SPM5 (http://www.fil.ion.ucl.ac.uk/spm) and Matlab 7.0®. The SPM5 unified segmentation algorithm (Ashburner & Friston, 2005) was used to generate probability maps of grey matter, white matter and cerebrospinal fluid for each individual. These were warped using DARTEL (Ashburner 2007), a high dimensional warping algorithm. The grey matter probability maps were modulated with the jacobian of the deformation to generate grey matter density. Because of our hypothesis implicating the hippocampus and parahippocampal gyrus, we used the WFU-Pick-Atlas toolbox to define these as regions of interest for our analysis. We further extracted grey matter volumes from subregions of the hippocampus and parahippocampus regions for our 18 subjects to investigate their relationship to memory performance (Amunts *et al.* 2005). Relevant volumes and grey matter voxels were used as measures to investigate correlations with individual memory performance in the main memory experiment.

3.1.4 Statistical Analysis

We used SPSS 14.0 and Microsoft Excel 2007 for all of the statistical analysis of our main memory experiment. We tested our data for parametric assumptions. Although no data met significance in the Shapiro-Wilk test, none of our data for our between-group analysis was normal when represented by histograms. Accordingly, we used non-parametric statistical tests for our between-group analyses, including the Mann-Whitney U test and Spearman's rank correlation coefficient. We used parametric tests when appropriate, including the Student's t-test, paired t-tests, bivariate

correlation, and various curve fitting techniques. We used Excel 2007 to analyze our pilot data.

3.2 Results

3.2.1 Whole-Group Analysis

We first analyzed the overall patterns of learning and forgetting with our subjects as a group. Using our words tested with the multiple choice pairs as a measure of recognition memory, it seems that memory improves over the first three sessions and declines subsequently. Using our repeated words as a measure of recall, there is a decline at the second session after which performance improves steadily. When plotted individually, our subjects had quite variable patterns of recognition memory performance over time. Curve fitting for logarithmic, exponential, growth, power, linear, or quadratic functions produced no R squared values over 0.3. Consequently, we analyzed performance in several ways. First we averaged all individual scores at each time point and plotted that against time. Next we tried mean correcting so as to compare between time points. For this, we took the mean of the scores at a time point, subtracted that mean from each individual score, and plotted those as well as the mean of the mean-corrected values. We also analyzed our scores in a piecewise fashion whereby we subtracted the mean score for all individuals at the n^{th} time point from the (n+1) time point, divided by time, and plotted these differences in order to see how the rates of forgetting and learning changed with time.

Recognition Memory – Averaged Scores at Each Time Point

Table 4 - **Descriptive Statistics**

	N	Mean	Std. Deviation
RecogOne	18	.57	.13
RecogTwo	18	.58	.06
RecogThree	18	.60	.12
RecogFour	16	.51	.10
RecogFive	18	.45	.10
Valid N (listwise)	16		

Recall – Averaged Scores at Each Time Point

Table 5 - **Descriptive Statistics**

	N	Mean	Std. Deviation
RecallCued1	18	.31	.15
RecallCued2	18	.42	.21
RecallCued3	18	.50	.23
RecallCued4	14	.53	.22
Valid N (listwise)	13		

Other Memory Measures: Forward Digit Span, Backward Digit Span, Order Memory, Spatial Memory, and Modified Words (Pattern Recognition)

Table 6 - **Descriptive Statistics**

	N	Mean	Std. Deviation
FDS	18	9.9	1.44
BDS	18	8.18	2.11
Order	17	9.86	2.32
Spatial	15	.51	.09
Modified	15	.68	.125
Valid N (listwise)	14		

We fit our data with various functions: logarithmic, exponential, growth, linear, and quadratic. The quadratic function fit the individual data as a group the best for both recognition and recall with R squared values of .212 and .113, respectively. When both measures were modeled together, the R squared value was .213, again for a quadratic function. Modeling the curve when recognition memory performance was averaged at each time point yielded a 2-order polynomial function with R squared value of .9202. When recall performance was averaged at each time point, a 2-order polynomial function fit the curve with an R squared value of .8525. We also fit each individual separately for both recognition and recall. Both quadratic and cubic functions fit our individuals. We propose that the decline at the second session is due to the design of our study; subjects were tested on these words immediately, and then 1.5 hours after encoding. Thus, performance at the first session would be better than performance at the second since much less time had passed between encoding and testing in the former than in the latter.

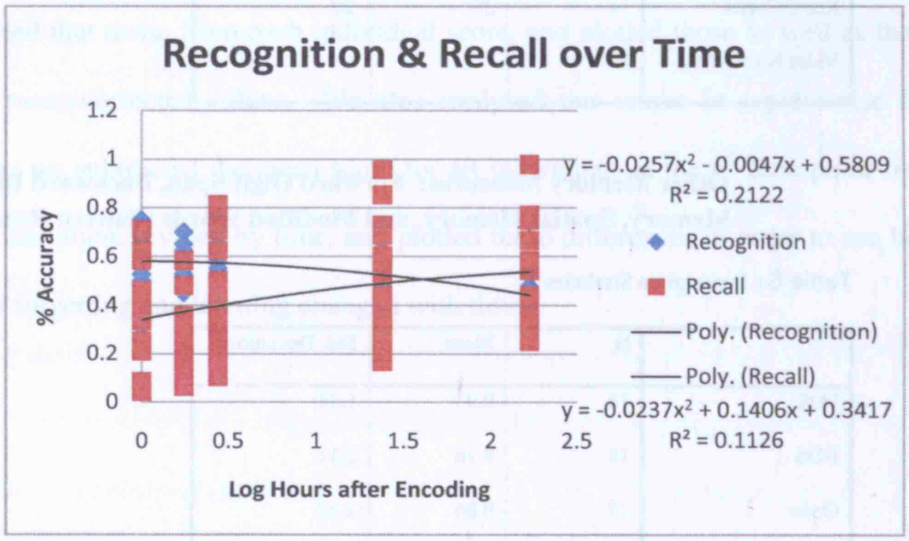


Figure 5

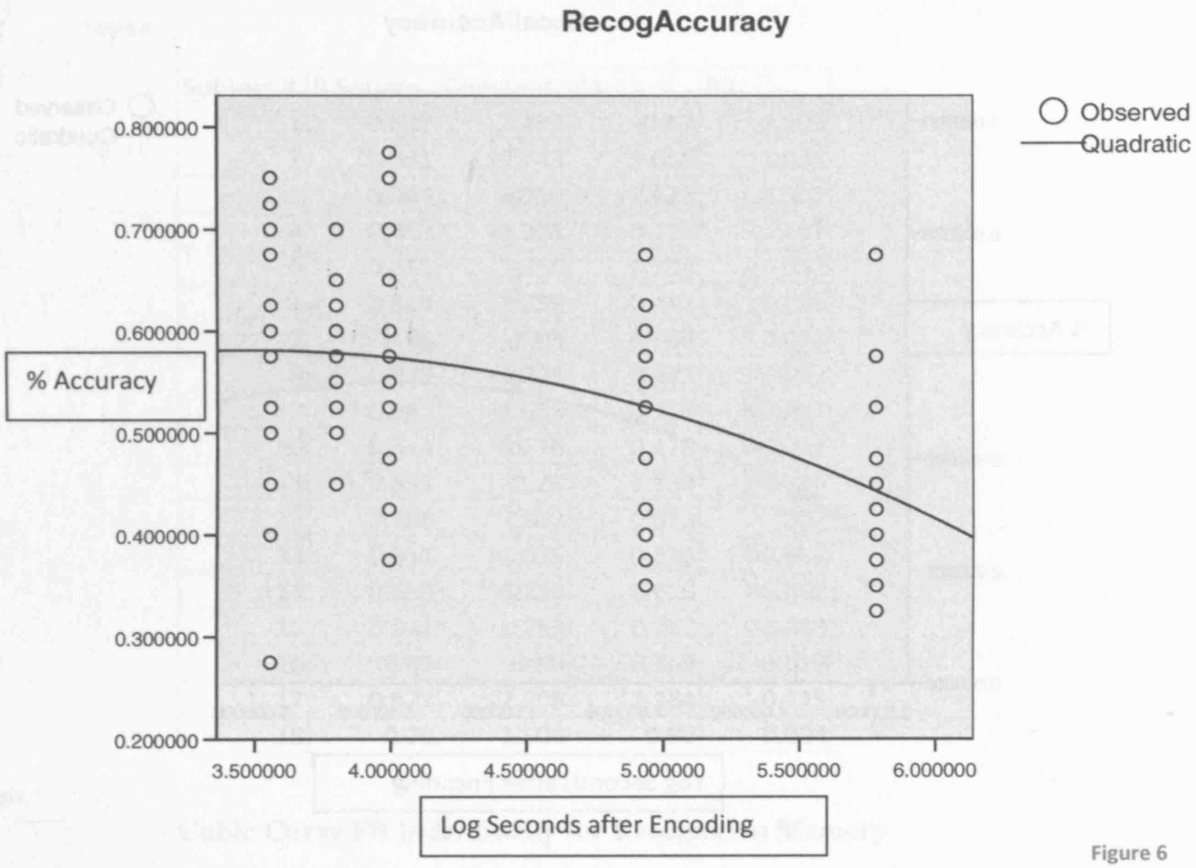

RecogAccuracy
Observed
Quadratic
% Accuracy
0.800000
0.700000
0.600000
0.500000
0.400000
0.300000
0.200000
3.500000
4.000000
4.500000
5.000000
5.500000
6.000000
Log Seconds after Encoding

Figure 6

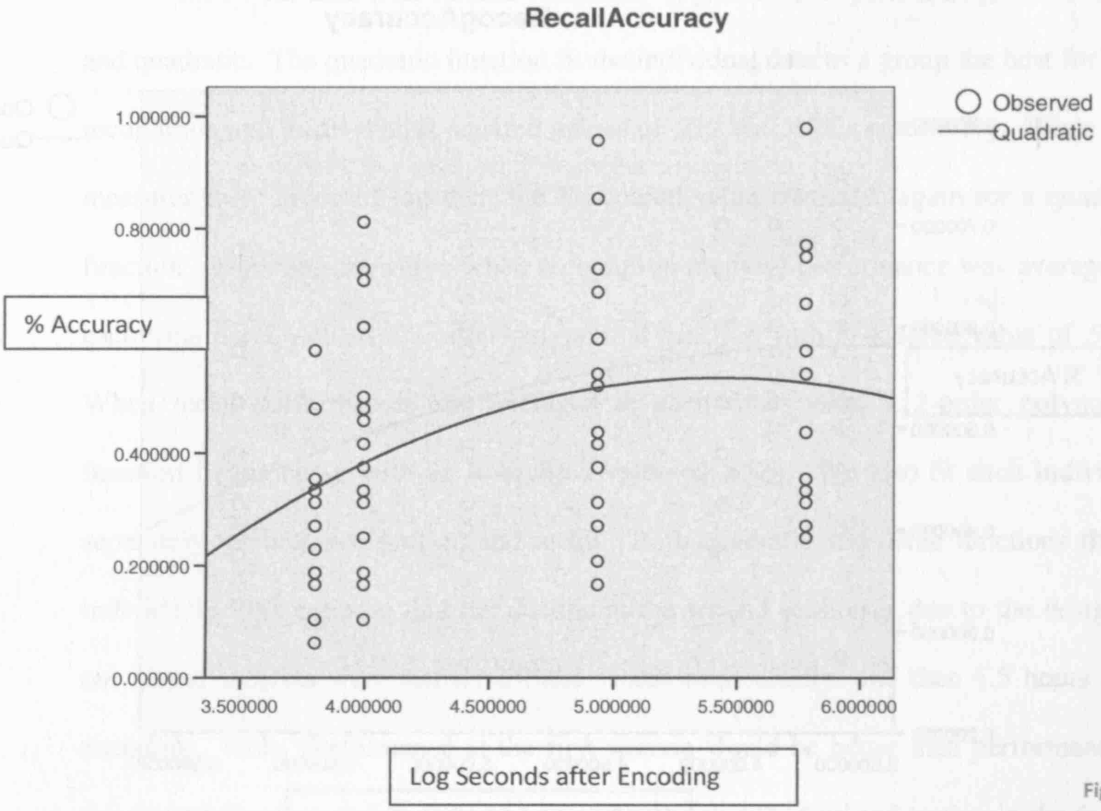


Figure 7

Parameter Estimates for Quadratic Model Fit

Table 7

	Equation	R Square	F	Constant	B1	B2
Recognition	Quadratic	.212	11.447	.272	.178	-.026
Recall	Quadratic	.141	5.348	-1.655	.807	-.074

Quadratic Curve Fit Individually for Recognition Memory

Table 8

Subject #	R Square	Constant	B1	B2
1	0.812	1.433	-0.67	0.105
2	0.881	19.743	-9.056	1.031
3	0.947	6.019	-2.673	0.301
4	0.692	-1.328	0.722	-0.07
5	0.855	-1.258	0.704	-0.062
6	0.818	1.259	-0.447	0.056
7	0.85	-1.93	0.963	-0.091
8	0.979	-1.178	0.621	-0.062
9	0.941	-1.639	0.776	-0.063
10	0.313	0.076	0.175	-0.022
11	0.855	-2.29	1.133	-0.114
12	0.786	-1.362	0.813	-0.07
13	0.911	-1.075	0.535	-0.047
14	0.688	-1.226	0.616	-0.062
15	0.941	-1.783	0.752	-0.068
16	0.95	-0.59	0.259	-0.019
17	0.627	-2.208	1.184	-0.115
18	0.78	-1.506	0.92	-0.094

Cubic Curve Fit Individually for Recognition Memory

Table 9

Subject #	Rsquare	Constant	B1	B2	B3
1	0.811	0.801	-0.221	0	0.008
2	0.881	19.743	-9.056	1.031	0
3	0.947	6.019	-2.673	0.301	0
4	0.694	-0.967	0.444	0	-0.006
5	0.855	-1.258	0.704	-0.062	0
6	0.81	0.841	-0.179	0	0.004
7	0.853	-1.303	0.545	0	-0.007
8	0.982	-0.749	0.335	0	-0.004
9	0.943	-0.123	0.496	0	-0.005
10	0.321	0.326	0	0.018	-0.003
11	0.868	-1.518	0.614	0	-0.008
12	0.789	-0.903	0.499	0	-0.005
13	0.912	-0.751	0.319	0	-0.003
14	0.703	-0.81	0.335	0	-0.005
15	0.941	-1.783	0.752	-0.068	0
16	0.95	-0.59	0.259	-0.019	0
17	0.636	-1.444	0.666	0	-0.008
18	0.78	-1.506	0.92	-0.094	0

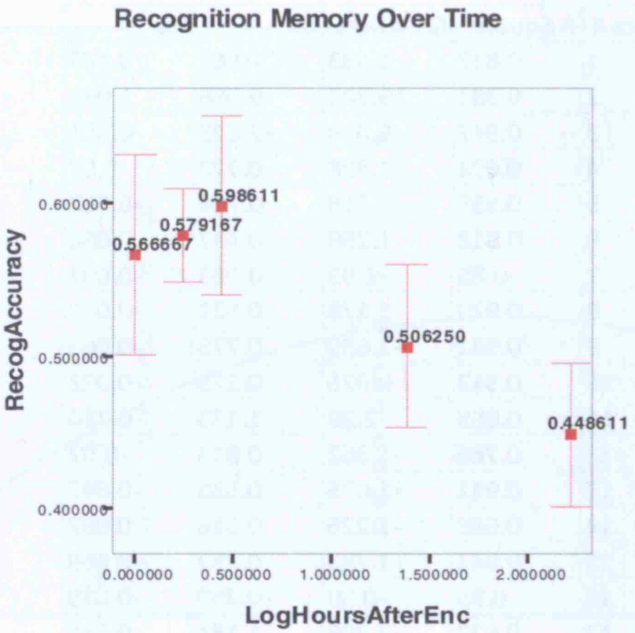


Figure 8

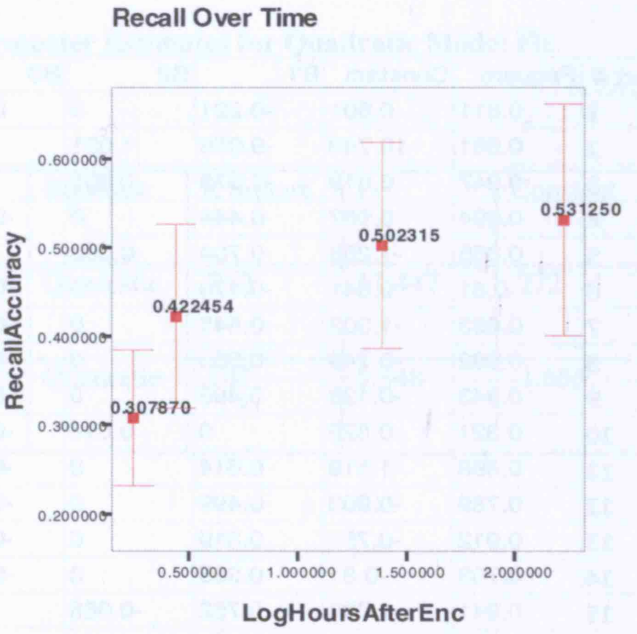


Figure 9

We used paired t-tests to compare in a piecewise fashion how different performance is between time points. We used the averaged scores as input, and did this for both recognition memory and recall. For recall, performance is significantly different between all sessions except between 24 hours (session 4) and 1 week (session 5) (p=.804). This indicates that significantly less learning occurs during this longer period of time. For recognition, it is only between session 3 and 24 hours (session 4) that there is a significant difference in performance (p=.000). This indicates that it is during the overnight period when most forgetting occurs. This is interesting because intuitively, it might seem that most forgetting would occur between the 24 hour and 1 week period.

Paired Samples Test for Recognition and Recall across Sessions

Table 10

Pair	t	Sig (2-tail)		Pair	t	Sig (2-tail)
				Rec1-2	-.550	.589
Recall1-2	-6.829	.000		Rec2-3	-1.022	.321
Recall2-3	-5.430	.000		Rec3-4	5.015	.000
Recall3-4	.253	.804		Rec4-5	1.691	.111
Recall1-4	-6.145	.000		Rec1-5	3.449	.003

We plotted the difference between sessions divided by time against session in order to obtain a forgetting rate (recognition memory) and a learning rate (recall). For repeated words, the learning rate over time followed a quadratic function: it peaks and then declines subsequently. The forgetting rate follows quite a different pattern over time. There is an initial increase, then a decrease, and then an increase again. This

parallels the pattern described above for absolute performance. That is, performance increased until session 3 and declined subsequently.

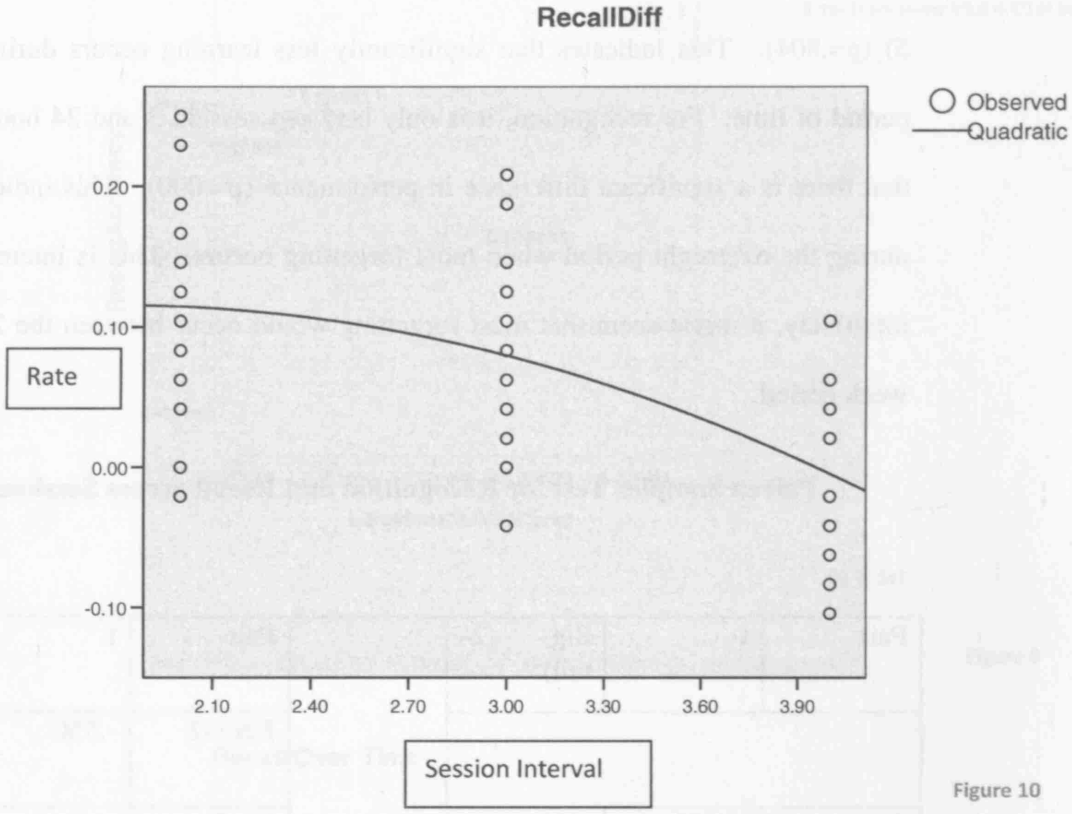


Figure 10

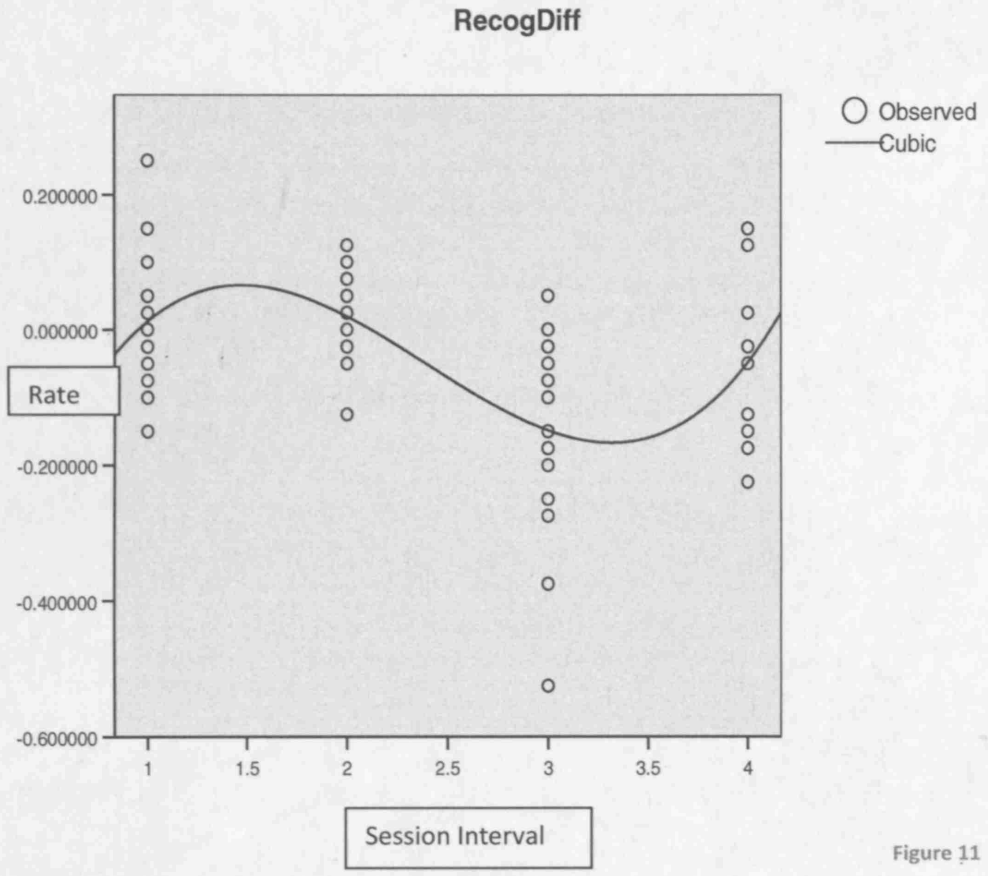


Figure 11

Curve Fitting for Differences between Time Points

Table 11

	Equation	R Square	F	Constant	B1	B2	B3
Recall	Quadratic	.355	12.944	.035	.089	-.025	…
Recog	Cubic	.290	8.999	-.613	1.082	-.531	.074

We ran several bivariate correlations across and between our memory measures in order to see if performance could be predicted for any of them. Additionally, such correlations may provide insight about similar processes shared between correlated measures. Performance on recognition and recall was significantly correlated across all time points except at 1 week (session5). Because both measures are highly correlated

and rely on different processes (recognition more demanding on encoding ability and recall more so for retrieval), they are similarly strong indicators of general memory ability.

During the immediate retrieval session, we asked subjects to recall at which position in the encoding list a word was seen. The aim of this test was to tap into explicit memory processes. We did a bivariate correlation analysis across this measure of order memory, and with all of the pairs and repeated words across all sessions. We did not observe a significant primacy or recency effect in this task. Performance on almost all measures across time points was significantly correlated with performance on order memory. The correlation decreased over time for recognition memory which indicates interference increased over time. Forward digit span was significantly correlated with performance on recognition memory immediately ($p=.031$) and at 24 hours ($p=.047$). In contrast, backward digit span, a task that requires more executive function, was not correlated with recognition memory at any time point. This is surprising given that forward digit span and backward digit span are highly correlated with each other ($p=.001$). Neither measure of digit span was significantly correlated with recall at any time point.

Performance on the spatial memory task was not significantly correlated with recognition memory or recall. However, performance on the modified word task was significantly correlated for both measures at almost all time points except 1 week for recognition.

Bivariate Correlation between Recall and Recognition Memory

Table 12

		Rep1	Rep2	Rep3	Rep4	Rep5
Recog1	Pearson	0.454	0.771	0.815	0.802	0.816
	Sig (2-tail)	0.067	0	0	0	0
Recog2	Pearson	0.435	0.568	0.642	0.67	0.608
	Sig (2-tail)	0.081	0.014	0.004	0.002	0.021
Recog3	Pearson	0.506	0.665	0.76	0.802	0.81
	Sig (2-tail)	0.038	0.003	0	0	0
Recog4	Pearson	0.628	0.536	0.593	0.586	0.662
	Sig (2-tail)	0.012	0.032	0.015	0.017	0.01
Recog5	Pearson	0.272	0.362	0.403	0.416	0.291
	Sig (2-tail)	0.291	0.14	0.097	0.086	0.313

Bivariate Correlation between Digit Span and Recognition Memory

Table 13

		FDS	BDS	Recog1	Recog2	Recog3	Recog4	Recog5
FDS	Pearson	1	0.715	0.508	0.218	0.101	0.504	0.046
	Sig (2-tail)		0.001	0.031	0.385	0.689	0.047	0.858
BDS	Pearson	0.715	1	0.235	0.048	-0.019	0.284	0.173
	Sig (2-tail)	0.001		0.349	0.851	0.939	0.287	0.492

Bivariate Correlation between Other Memory Measures and Recognition Memory

Table 14

		Recog1	Recog2	Recog3	Recog4	Recog5
Order	Pearson	-0.778	-0.555	-0.681	-0.569	-0.27
	Sig (2-tail)	0	0.021	0.003	0.027	0.295
Spatial	Pearson	-0.051	0.117	0.014	0.178	0.137
	Sig (2-tail)	0.857	0.679	0.96	0.525	0.626
Modified	Pearson	0.816	0.699	0.614	0.751	0.149
	Sig (2-tail)	0	0.004	0.015	0.001	0.596

Bivariate Correlation between Other Memory Measures and Recall Memory

Table 15

		Rep1	Rep2	Rep3	Rep4	Rep5
Order	Pearson	-0.307	-0.757	-0.819	-0.819	-0.736
	Sig (2-tail)	0.231	0	0	0	0.004
Spatial	Pearson	-0.179	-0.07	-0.046	-0.068	0.024
	Sig (2-tail)	0.541	0.803	0.87	0.809	0.934
Modified	Pearson	0.709	0.643	0.679	0.683	0.701
	Sig (2-tail)	0.005	0.01	0.005	0.005	0.005

Parsing apart the different memory processes that contribute to recognition memory performance, we examined the percent accuracy of each of the five multiple choice answers. Next, we combined answers one and two and compared them with answers three and four in order to compare associative memory versus item memory. Associative memory is more a measure of recollection whereas item memory provides a measure of familiarity (Yonelinas 2002). Pairs of the third type expectedly had the worst performance as single Swahili words would be the most difficult to recognize.

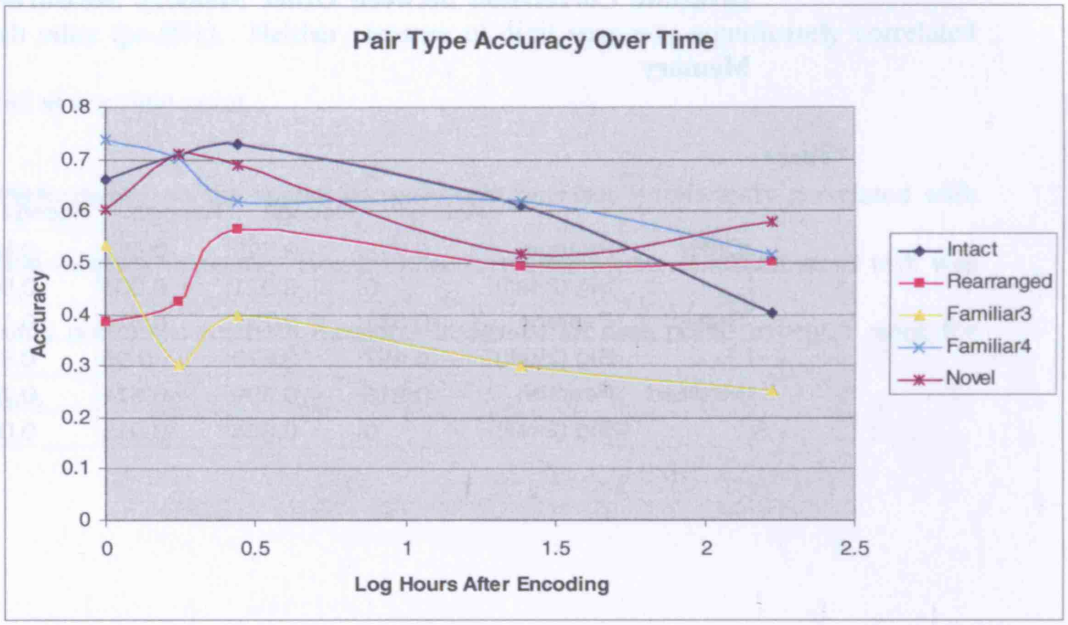


Figure 12

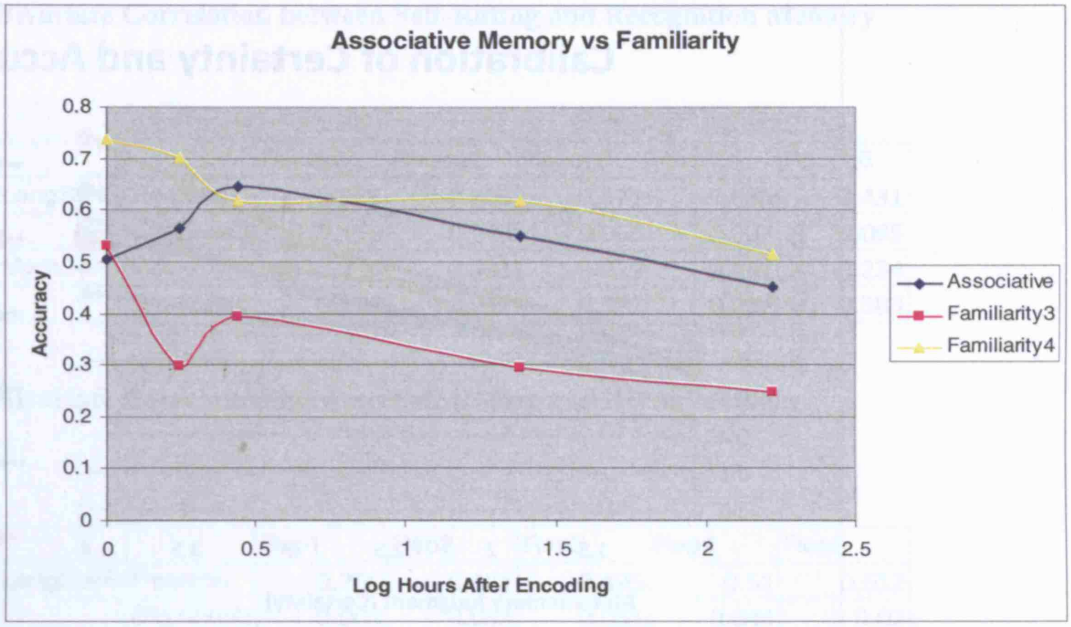


Figure 13

Finally, we have an explicit measure of metamemory: after subjects made their choices on the multiple choice pair task, they were asked to make a retrospective certainty judgment of their answers. We did a between-subject comparison to determine the degree to which confidence and accuracy are related. We plotted how the different certainty levels changed over time, and how percent accuracy at each certainty level changed over time. Certainty and accuracy had the expected relationship: where subjects felt the most certain of their answers, they were more likely to be correct.

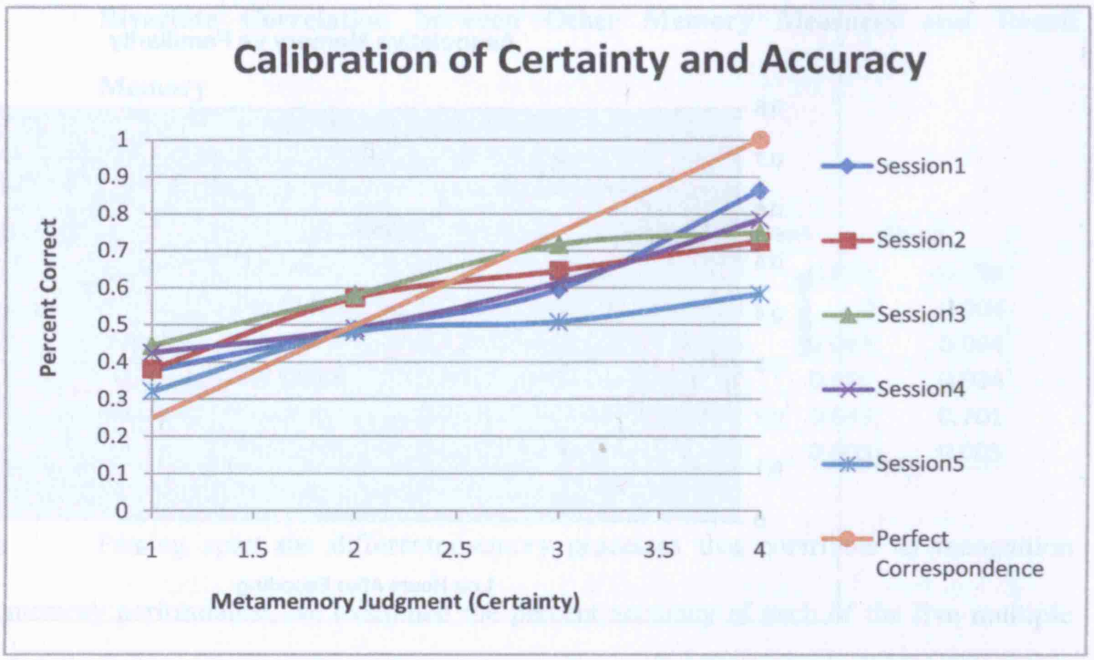


Figure 14

Linear Regression Relating Certainty with Accuracy

Table 16

Session	Coefficient	Intercept	R^2
1	0.47	0.35	0.94
2	0.33	0.42	0.94
3	0.31	0.47	0.94
4	0.36	0.4	0.96
5	0.24	0.35	0.9

At the end of the study, we asked subjects to rate how well they thought they learned languages compared with others. This self-rating of language ability was significantly correlated at all measures of recall but at only 24 hours for recognition (p=.007). Curiously, the self-rating for memory ability was not correlated for either recognition or recall performance, although it was quite close immediately (p=.054) and at 1 week (p=.054).

Bivariate Correlation between Self-Rating and Recognition Memory

Table 17

		Recog1	Recog2	Recog3	Recog4	Recog5
LangSelfR	Pearson	0.375	0.306	0.471	0.688	0.431
	Sig (2-tail)	0.152	0.248	0.066	0.007	0.095
MemSelfR	Pearson	0.293	0.331	0.359	0.461	0.234
	Sig (2-tail)	0.271	0.211	0.172	0.097	0.383

Bivariate Correlation between Self-Rating and Recall Memory

Table 18

		Rep1	Rep2	Rep3	Rep4	Rep5
LangSelfR	Pearson	0.706	0.491	0.495	0.51	0.612
	Sig (2-tail)	0.003	0.053	0.051	0.044	0.02
MemSelfR	Pearson	0.507	0.407	0.383	0.365	0.525
	Sig (2-tail)	0.054	0.118	0.144	0.165	0.054

3.2.2 Between-Group Analyses

Again, the scores for recall and recognition memory met the conditions for normality according to the Shapiro-Wilk test but failed when represented with histograms. For Kibra, ten individuals were CT/TT and seven were CC. We compared groups with the Mann-Whitney U statistic. For recall, we found the expected trend; namely that the T allele confers better memory performance, but we failed to reach significance. For recognition, T carriers performed better for sessions 1, 2 and 5 but worse on 3 and 4. However, the *p* values for these latter comparisons were quite high. We plotted the difference in performance between time points for the repeated words in order to get a measure of learning rates. The CT & TTs learned faster over the first three time points but by 24 hours, the CCs had caught up and subsequently both groups showed nearly identical learning rates. No difference between groups was found for the modified word task or the spatial memory task but subjects with the T allele performed best.

Kibra – 2.5% Agarose Gel

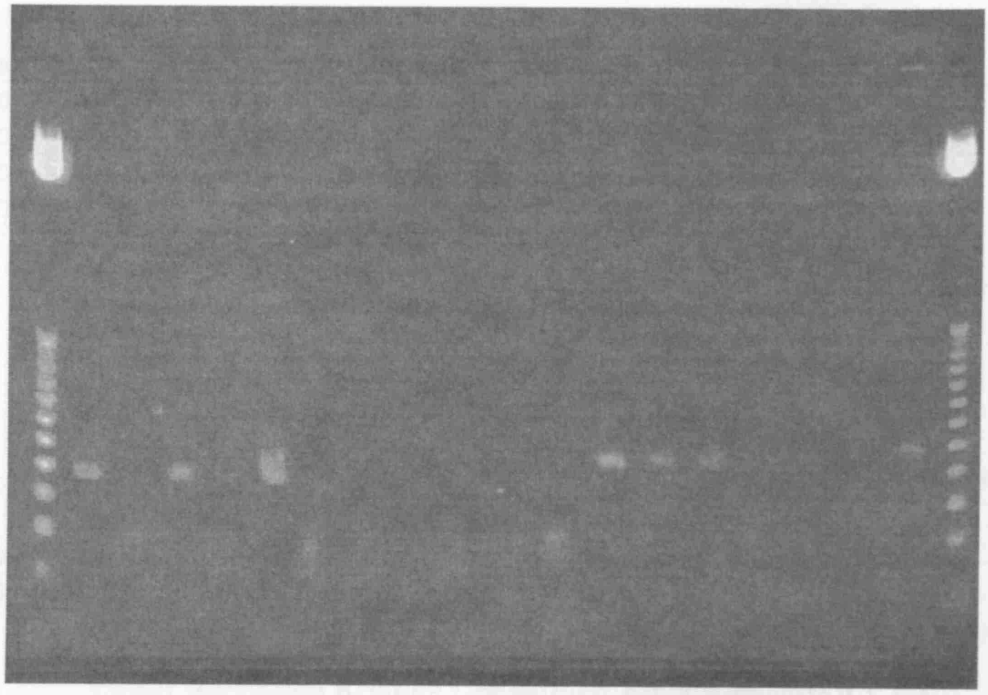


Figure 15

Virtual Gel

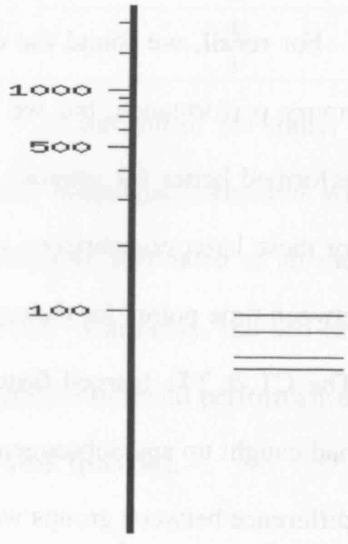


Figure 16

(derived from Nebcutter)

Kibra: CC vs CT+TT for Recognition and Recall

Table 19

Measure	CC vs CT+TT	Session1	Session2	Session3	Session4	Session5
Recognition	Mann-Whitney U	34	33	32	25	25.5
	Sig (2-tail)	0.847	0.769	0.699	0.727	0.309
Recall	Mann-Whitney U	31.5	29	25.5	26	16
	Sig (2-tail)	0.958	0.498	0.312	0.334	0.474

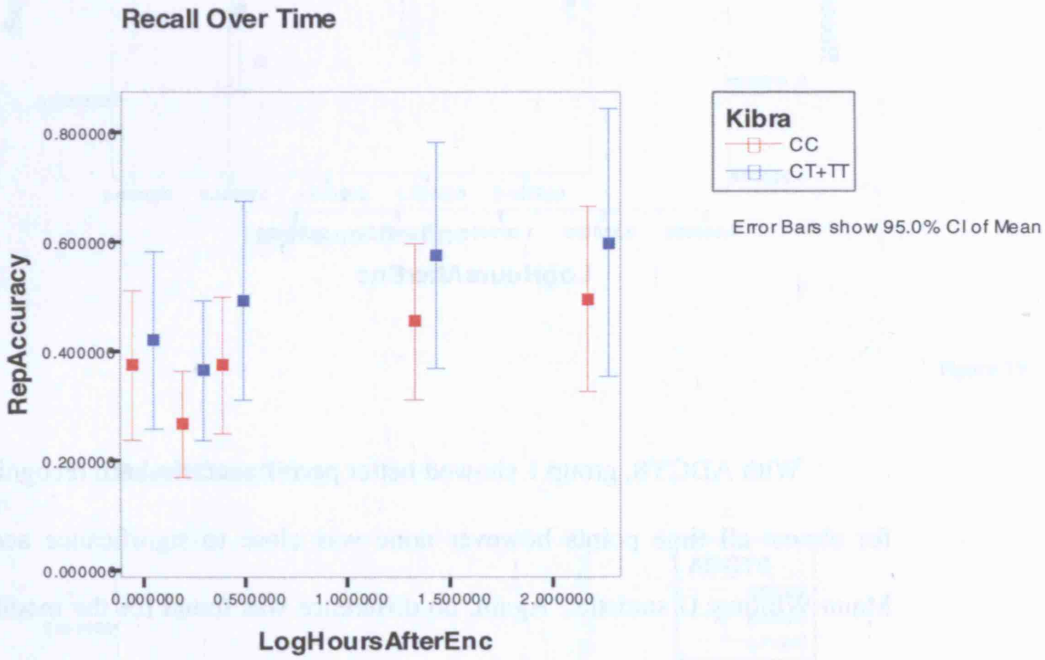


Figure 17

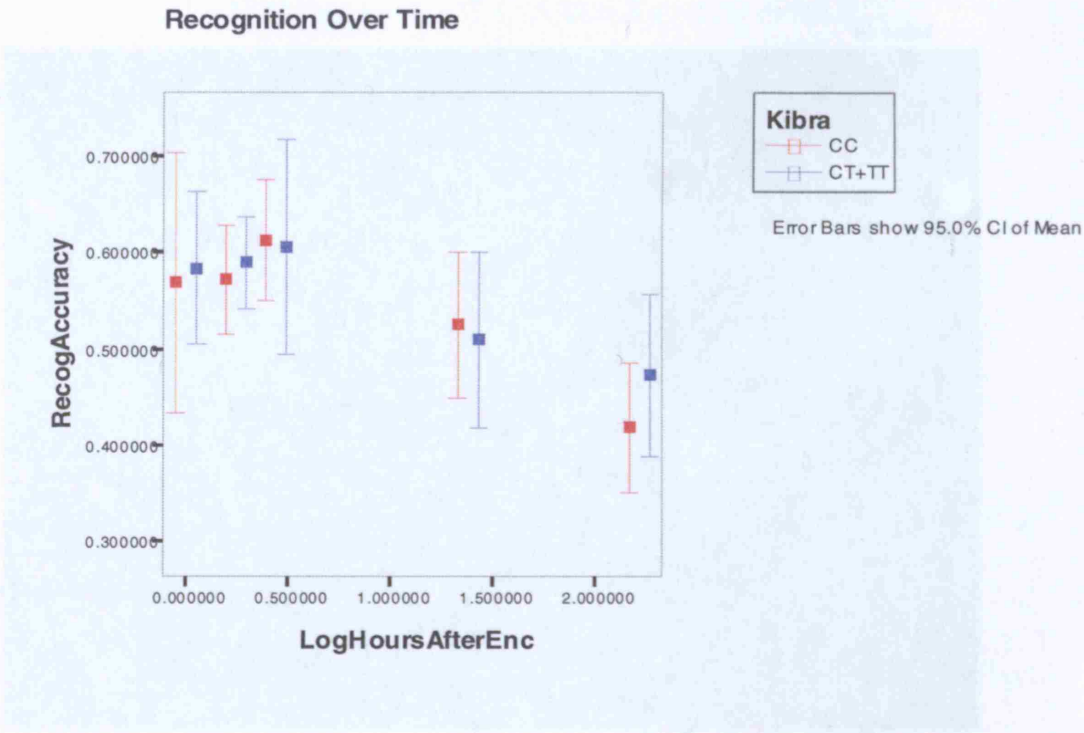


Figure 18

With ADCY8, group 1 showed better performance in both recognition and recall for almost all time points however none was close to significance according to the Mann-Whitney U statistic. Again, no difference was found for the modified word task or the spatial memory task but group 1 and 3 performed best on both tasks. Overall, groups 1 and 3 performed comparably on all measures while group 2 (the heterozygotes) was consistently the worst.

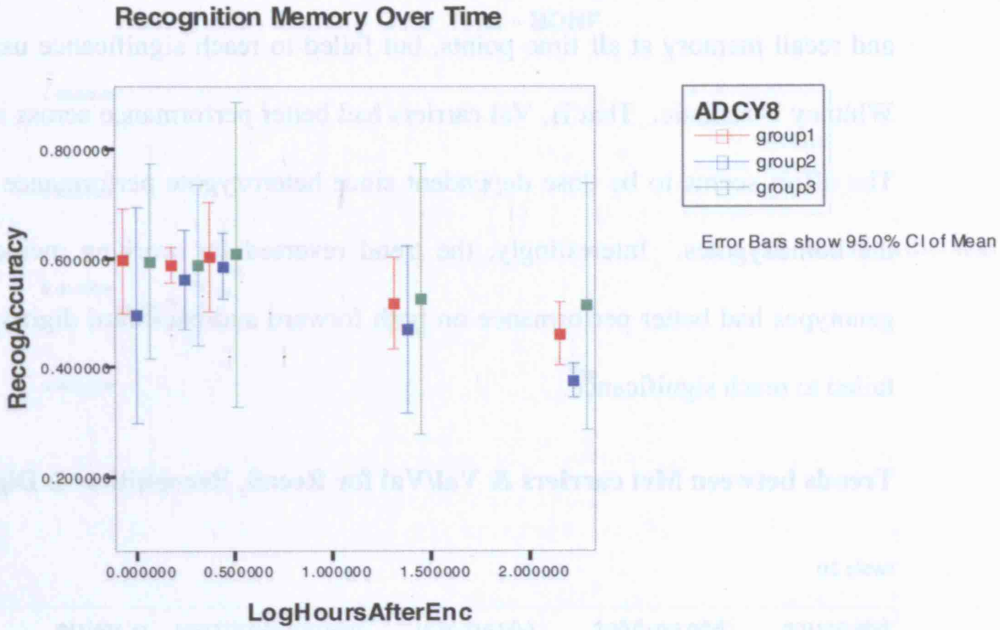


Figure 19

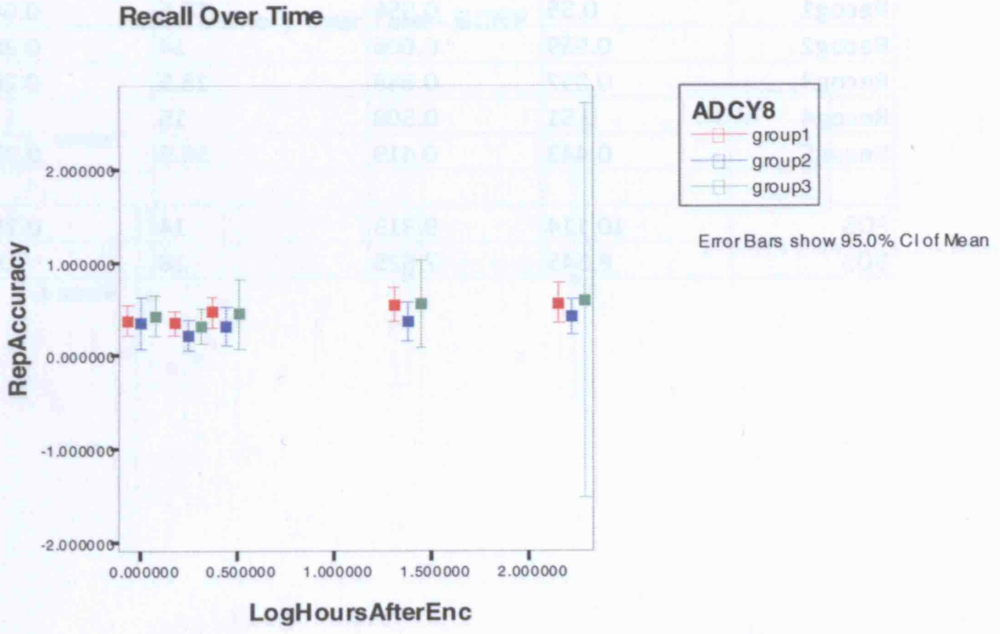


Figure 20

Concerning our third gene BDNF, we found the expected trend for recognition and recall memory at all time points, but failed to reach significance using the Mann-Whitney U statistic. That is, Val carriers had better performance across all time points. The effect seems to be dose dependent since heterozygote performance is in between the homozygotes. Interestingly, the trend reversed for working memory. Met/Met genotypes had better performance on both forward and backward digit span, but again failed to reach significance.

Trends between Met carriers & Val/Val for Recall, Recognition & Digit Span

Table 20

Measure	Mean-Met	Mean-Val	Mann-Whitney	*p* value
Recall1	0.286	0.292	20	0.793
Recall2	0.39	0.406	22	1
Recall3	0.462	0.464	20.5	0.844
Recall4	0.495	0.521	10.5	0.578
Recog1	0.55	0.556	18.5	0.647
Recog2	0.559	0.606	14	0.289
Recog3	0.557	0.638	13.5	0.265
Recog4	0.51	0.508	15	1
Recog5	0.443	0.419	14.5	0.323
FDS	10.114	9.313	14	0.291
BDS	8.545	7.625	18	0.6

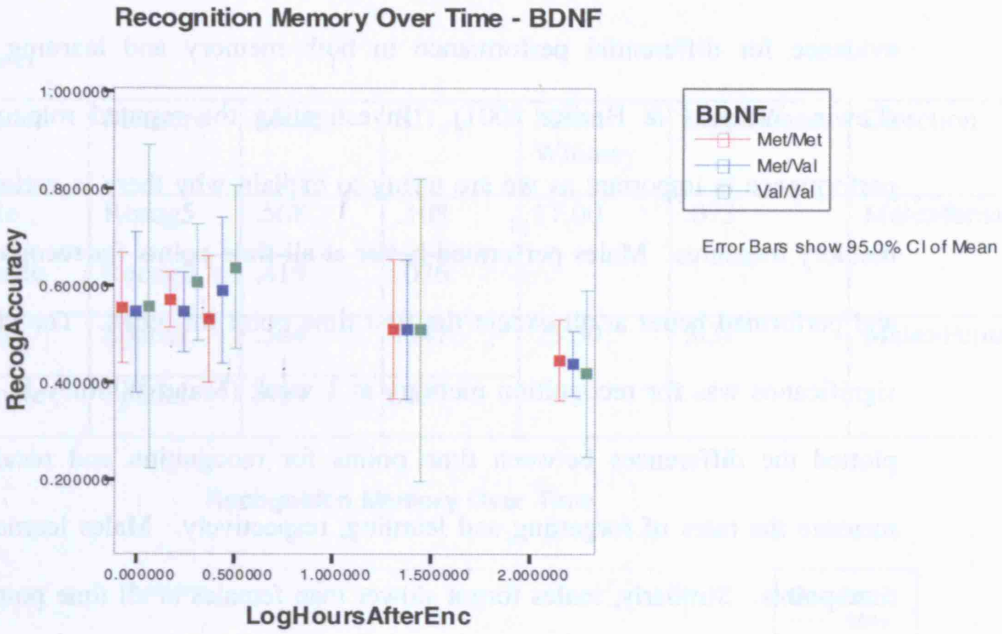


Figure 21

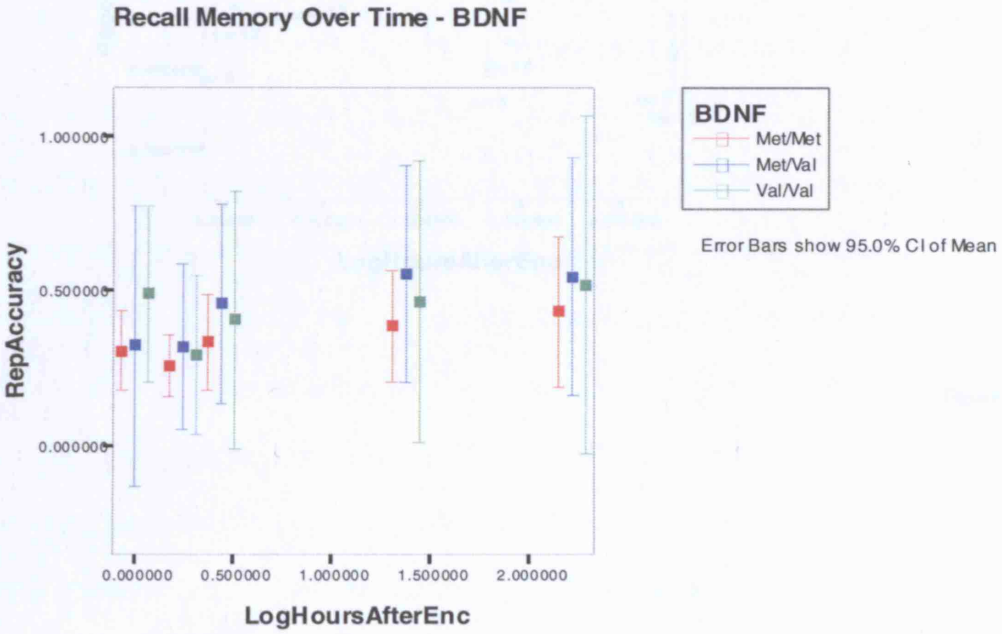


Figure 22

We investigated gender differences between memory measures because there is evidence for differential performance in both memory and learning of languages (Lewin, Wolgers & Herlitz 2001). Investigating the reputed role of gender and performance is important as we are trying to explain why there is variability between memory measures. Males performed better at all time points for recognition memory, and performed better at all except the first time point for recall. The closest value to significance was for recognition memory at 1 week (Mann-Whitney U, p=.073). We plotted the differences between time points for recognition and recall in order to measure the rates of forgetting and learning, respectively. Males learned faster at all time points. Similarly, males forgot slower than females at all time points. However, none of these differences at any time point was significant. Lastly, males performed better on the spatial memory task (Mann-Whitney U, p=.031) while females performed better on the modified word task, but not significantly.

Gender: Significant Differences by Mann-Whitney U Statistic

Table 21

Gender	Measure	Mean	SD	Mann-Whitney	Significance	Direction
Male	Recog5	.508	.108	17.00	.073	Male>female
Female	Recog5	.419	.076			
Male	Spatial	.564	.047	75.50	.031	Male>Female
Female	Spatial	.484	.097			

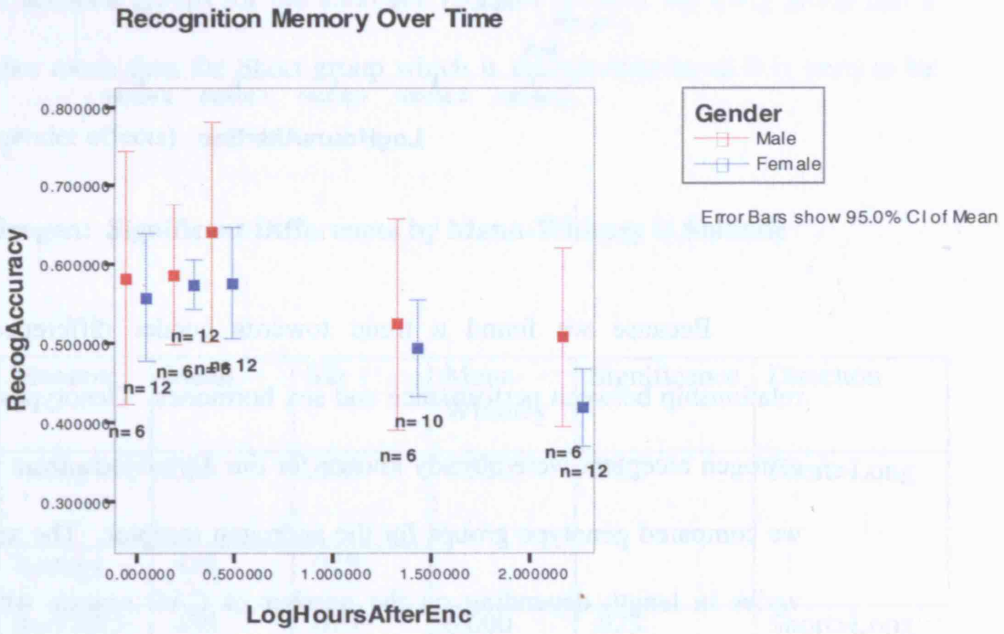


Figure 23

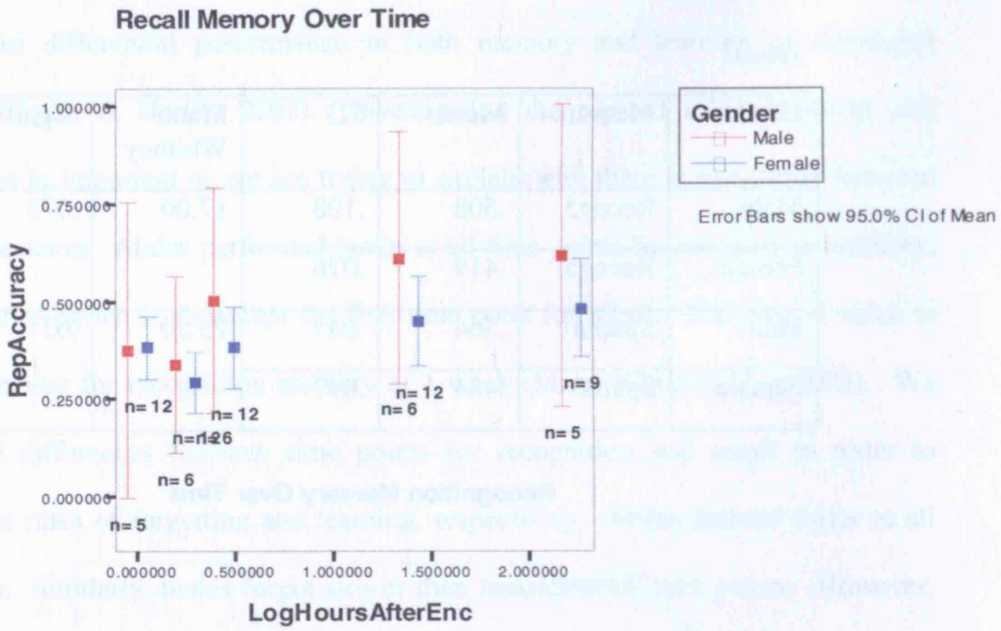


Figure 24

Because we found a trend towards gender difference, we examined the relationship between performance and sex hormones. Genotypes for the androgen and estrogen receptors were already known for our 18 subjects from previous work. First, we compared genotype groups for the androgen receptor. The androgen receptor gene varies in length depending on the number of CAG repeats which subtly modulates testosterone levels (Edwards, Hammond, Jin, Caskey & Chakraborty 1992). We divided our subjects into two groups based on the median length of the receptor (22 residues): 'short' and 'long'. Subjects with the shorter receptor performed better on both recognition and recall at all sessions, and reached significance for recognition memory performance at 24 hours (Mann-Whitney U test, p=.042). There was also a significant difference when we compared performance on recognition memory between sessions 5 and 1 (p=.023). Interestingly, there was almost a significant difference in performance for the modified word task (Mann-Whitney U test, p=.051). We did the

same for the estrogen receptor. Subjects with the longer receptor performed better at all time points for recall, but there was no clear trend between genotypes for recognition memory.

Despite our decision to investigate the sex hormone receptors being well motivated, it seems unlikely that the differences in performance between genotypes underlie the differences found with gender. For instance, there was a large difference between gender for performance on spatial memory (males>females) but no significance between groups for the androgen receptor (in fact, the Long group had a slightly higher mean than the Short group which is the opposite trend if it were to be explaining gender effects).

Androgen: Significant Differences by Mann-Whitney U Statistic

Table 22

Androgen	Measure	Mean	SD	Mann-Whitney	Significance	Direction
Short (0/0.5)	Recog4	.534	.096	6.550	.042	Short>Long
Long (1)	Recog4	.419	.075			
Short (0/0.5)	RecDiff5-1	.438	.079	6.000	.023	Short>Long
Long (1)	RecDiff5-1	-.019	.066			
Short (0/0.5)	Modified	.705	.108	4.000	.051	Short>Long
Long (1)	Modifed	.537	.112			

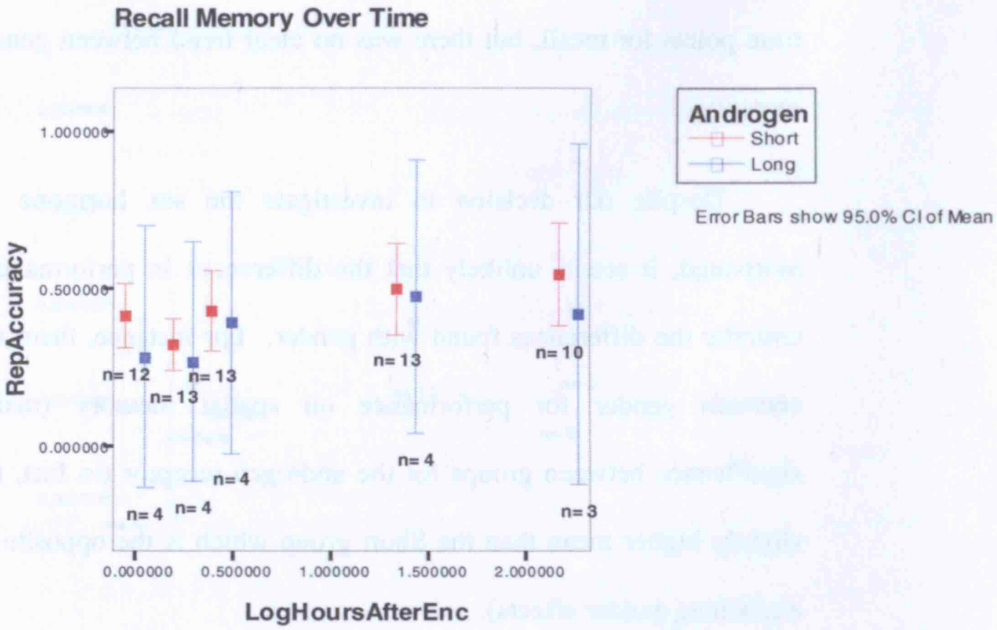


Figure 25

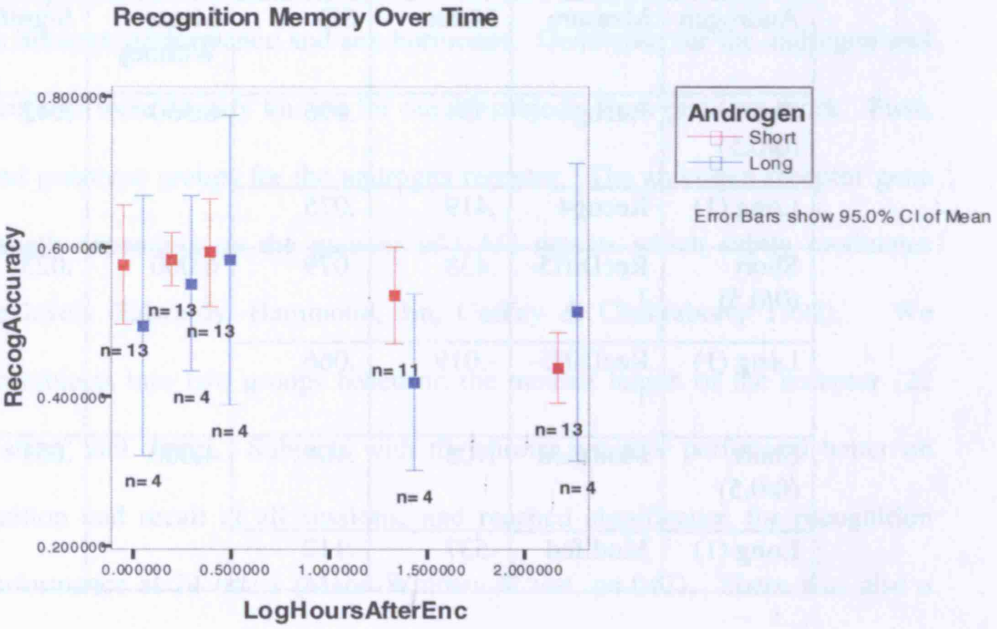


Figure 26

3.2.3 Voxel Based Morphometry

Because we found the expected trend for BDNF in our behavioural data, we hypothesized that some of BDNF's influence on memory performance could be due to its effect on brain structure. Further, because the trend between working memory and our other measures reversed for BDNF, we decided to investigate working memory and brain structure as well. First we analyzed how BDNF and working memory relate separately to brain structure, followed by how they may interact with each other. We conducted a VBM analysis with 206 individuals in our subject sample pool. We found that grey matter density correlates positively with forward digit span in the right parahippocampal gyrus and the dorsolateral prefrontal cortex bilaterally. It correlates negatively with the inferior cerebellum bilaterally (+-39, -61, -35) and left superior cerebellum (-19 -28 -33). Backward digit span correlates positively with right parahippocampal gyrus volume, but does not overlap with the forward digit span finding association in that region. This is interesting because backward and forward digit span strongly correlate with each other behaviourally but not structurally. Thus, some other common mechanism, neurotransmitter, or environmental factor must be underlying their behavioural relationship.

Positive Correlation between Forward Digit Span and Parahippocampal Gyrus

Table 23

p FWE-corr	T	Z	x - mm	y - mm	z - mm
0.029	4.01	3.92	29	-48	-4

Next, we conducted a VBM analysis with BDNF genotype. We found that Met carriers have significantly increased parahippocampal volume bilaterally, as compared with Val homozygotes. This region overlaps with the area associated with forward digit span and survives small volume correction.

Positive Correlation between Met Carriers and Parahippocampal Gyrus Volume

Table 24

p FWE-corr	T	Z	x - mm	y - mm	z - mm
0.027	3.77	3.7	23	-23	-23
0.057	3.52	3.47	-19	-32	-16
0.089	3.36	3.31	-19	-28	-25
0.573	2.45	2.43	-11	-6	-19

Parahippocampal Gyrus – BDNF

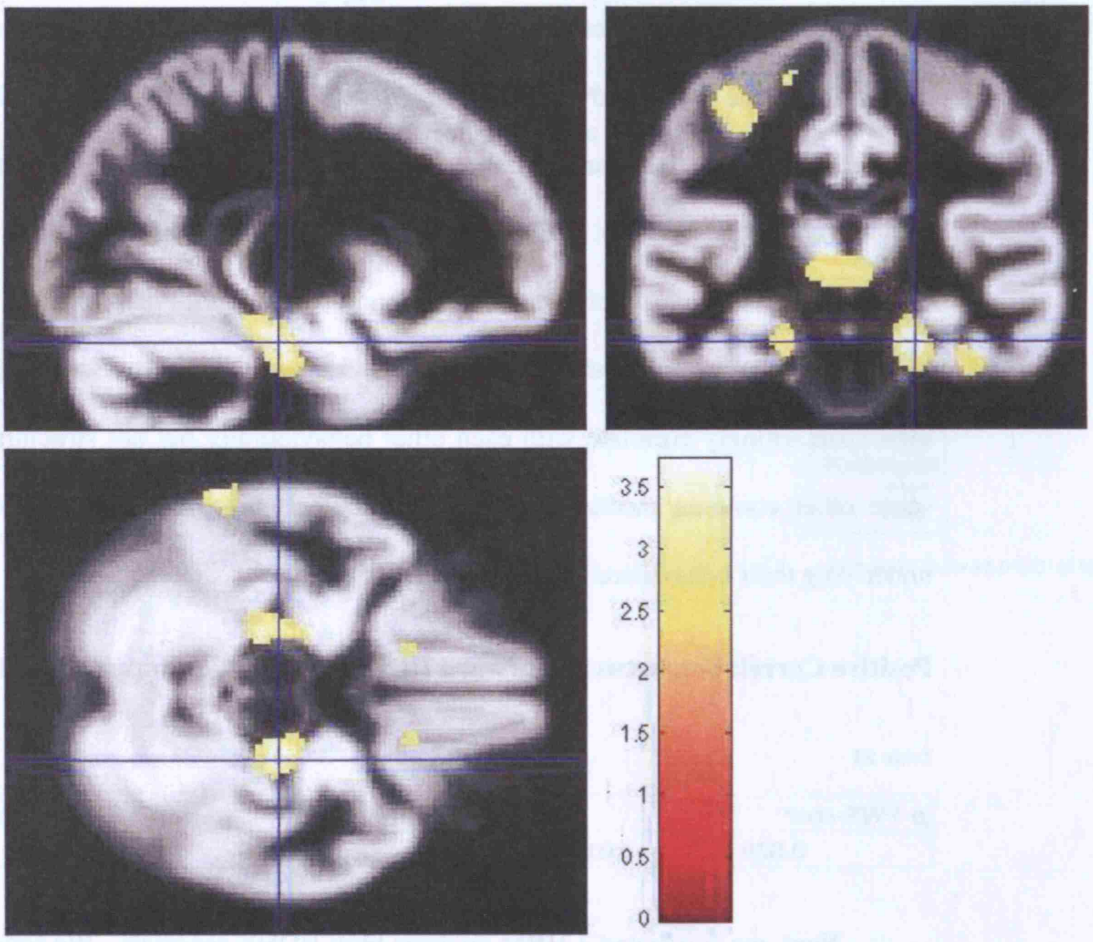


Figure 27

Anterior Parahippocampal Gyrus – Overlap between FDS and BDNF

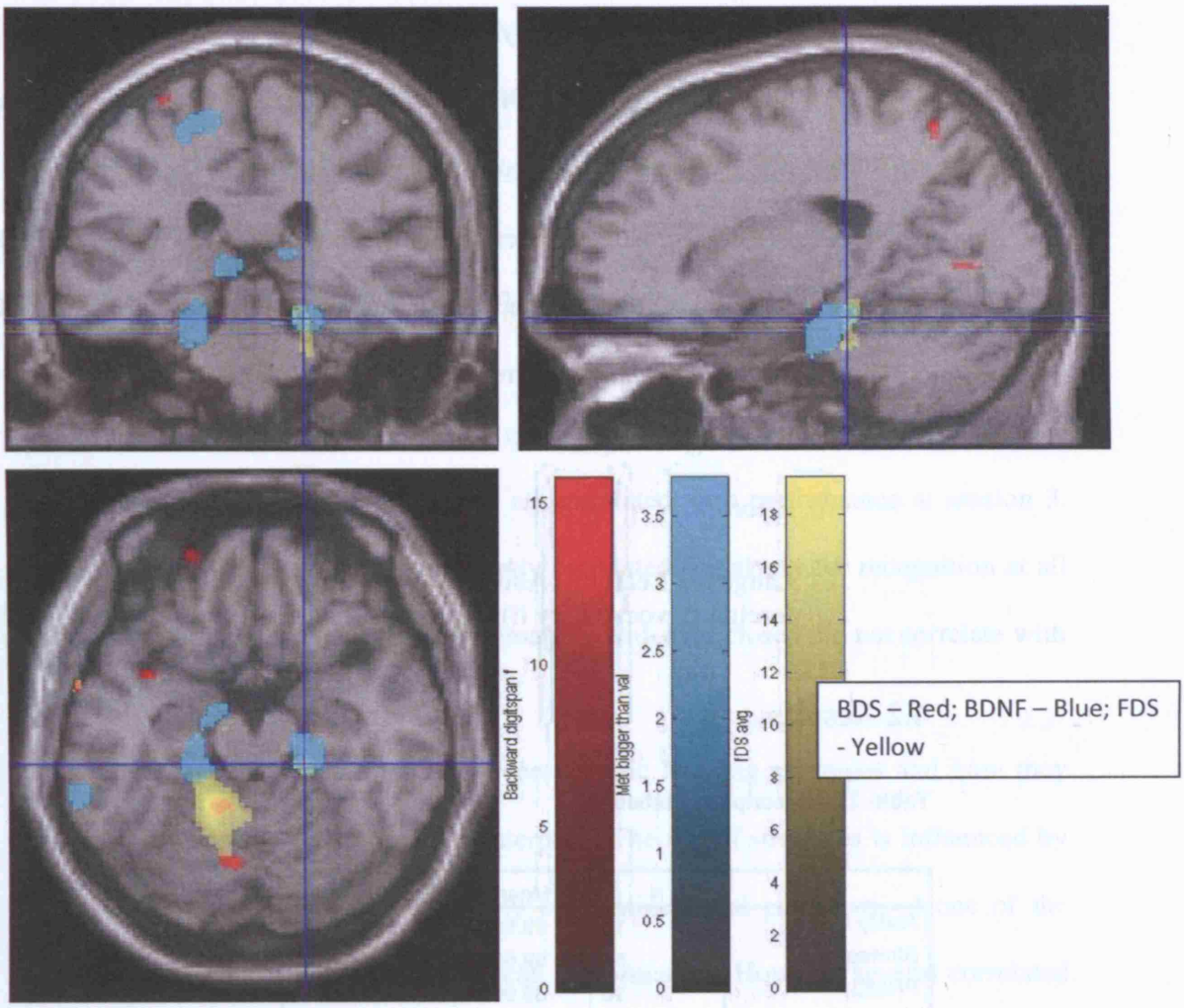


Figure 28

4. Follow-Up: Metamemory

4.1 Materials & Methods

We administered an online questionnaire to our subjects to expand upon the self-rating question and memory performance. We compiled our questions from a combination of standardized questionnaires and our own design (see Appendix). We sought several measures of metamemory:

1. Contentment with one's memory (Troyer & Rich 2002)
2. Overall Ability (Troyer & Rich 2002)

3. Strategies used (Troyer & Rich 2002)
4. Everyday Memory (Royle & Lincoln 2007)
5. Visual Imagery (with eyes opened and with eyes closed; VVIQ, http://www.staff.city.ac.uk/d.marks/vviq.htm)
6. PRMQ (provides an overall memory measure; Crawford *et al.* 2006)
7. Retrospective & Prospective Memory (PRMQ; Crawford *et al.* 2006)
8. Short-term & Long-term Memory (PRMQ; Crawford *et al.* 2006)
9. Learning Strategies
10. Effort
11. Language Learning Ability: as compared with others, how well one learns foreign i) vocabulary ii) grammar iii) accents and iv) languages in general

4.2 Results

Table 25 - **Descriptive Statistics**

	N	Mean	Std. Deviation
Ability	16	69.5625	11.27220
Strategy	16	59.6250	12.97626
PRMQ	16	36.0000	9.99333
Prospective	16	18.8750	5.66716
Retrospective	16	17.1250	5.18813
ShortTerm	16	18.3750	4.82873
LongTerm	16	17.1250	5.18813
VisImOpen	16	33.7500	11.95826
VisImClosed	16	37.1250	16.09503
MetaStrateg	15	30.0000	8.10643
MetaEffort	15	19.7333	7.85099
Valid N (listwise)	15		

Between metamemory measures, there were many correlations. This confirms consistency across the subjective judgments. Self-rating of memory ability correlated positively with everyday memory (p=.000), the PRMQ (p=.000), and visual imagery with eyes closed (p=.042). Visual imagery between eyes open and eyes closed was

unsurprisingly correlated positively (p=.001). All measures of the PRMQ (prospective, retrospective, short term, long term) were significantly correlated with each other.

Concerning the relationship between the self-ratings and the objective measures of memory performance from our study, there were many that reached significance. Ability, strategy, everyday memory, and visual imagery did not correlate with any of the recall sessions but retrospective, short term, and long term (PRMQ) did at sessions 2, 3 and 4.

Ability and strategy use did not correlate with recognition performance. The PRMQ measures and everyday memory all correlated with performance at session 3. Visual imagery with eyes open significantly correlated negatively for recognition at all but the last time points. However visual imagery with eyes closed did not correlate with recognition.

The few correlations found between specific learning strategies and how they related to performance are difficult to interpret. The use of strategies is influenced by many factors, and specific strategies rely on combinatorial processes. None of the strategies significantly correlated with recall performance. However several correlated with performance for recognition memory:

1) Memorizing where information is placed on the page was correlated with session 5 (p=.007)
2) Memorizing information by highlighting/circling/underlining in colour was correlated with session 3 (p=.034)
3) Repeating information in a cumulative fashion was correlated with session 3 (p=.002)

Self-rating of language learning ability was also correlated with performance on recognition memory at session 4. These measures included ability to learn new

vocabulary (p=.006), learn new grammar and structure (p=.016), and overall ability to learn languages (p=.006), but did not correlate with ability to pick up accents.

As for our other memory measures (digit span, order memory, spatial memory, and the modified word task), there were several correlations. Ability, strategies and everyday memory correlated with nothing. Digit span correlated positively with prospective and short term (PRMQ) measures. Modified words (pattern separation) correlated positively with retrospective and short term (PRMQ) measures. Order memory correlated positively with retrospective (p=.011), short term (p=.017) and long term (p=.011) (PRMQ) measures. Visual imagery with eyes open but not closed correlated positively with order (p=.038) but nothing else. Of all the language learning abilities enquired about, ability to learn foreign grammar related positively to the modified word task (p=.008).

5. Discussion

Apart from the genetic and cellular mechanisms that underlie memory performance, we considered many other factors that probably account for natural variability in human memory. Our pilot study provided information about how people best learn foreign vocabulary. Picture-matching seems to be the most efficient, and this may not be surprising since many popular language-learning software packages employ this method of learning, for example, the Rosetta Stone. However, learning by sentences was also quite robust and showed a different pattern of forgetting over time compared with the words learned and tested with pictures. It would be interesting to investigate gender trends with the different methods of encoding and retrieval. Such information about learning method effectiveness is practical as well since it is clear that not all individuals learn or remember in the same way. Uncovering the particular methods by which certain groups of individuals learn best does not make any statements about which group is the best, but rather serves to discover the best match between

method type and subsequent performance such that all individuals can learn most efficiently and to the best of their ability.

5.1 Within-Group Analysis

We embarked on this study from a hypothesis-driven approach to look at both remembering and forgetting. We sought to explain some of the variability between individuals by mapping it onto molecular processes though candidate genes. Looking across individuals, memory performance did not decline in the way that we had expected based on the literature (Rubin & Wenzel 1996). Rubin & Wenzel combed through 210 published data sets in order to find which retention function would best describe different types of memory. They found that memory decline over time is best described by a logarithmic function, a power function, an exponential in the square root of time, and a hyperbola in the square root of time (Rubin & Wenzel 1996). In contrast, our recognition memory scores clearly followed a second order polynomial function, first with an increase in performance, peaking at the third session, and then a steady decline. We are unsure how to explain our temporal pattern in performance. On the one hand, perhaps our unusual pattern of forgetting is due to our particular study design, or the set of stimuli used at each session. However the latter case is unlikely since we observed the same pattern in our pilot data, despite using different subsets of words. On the other hand, perhaps what we observe in our data is actually how forgetting proceeds over time. In fact, the time course of forgetting in individuals is quite variable. It was only when we averaged and mean corrected scores at each time point across all individuals that we were able to derive a 2-order polynomial as the function with the best fit. One reason for the variability in memory decline over time between individuals could be when in the day with respect to sleep they performed our experiment. Sleep is known to influence forgetting, either by preventing interference or by enhancing

consolidation (Walker 2005, Wixted 2004). It would be interesting to include another time point at 12 hours, and to divide our group by retrieval sessions before or after sleep to observe any associations with performance.

Performance was significantly correlated between most of our memory measures. The correlation between recognition and recall performance indicates both are a strong measure of general memory ability. However, each has a different time course of forgetting. Difference between sessions was only significant between sessions 3 and 4 (24 hours) for recognition memory, indicating that recognition memory is strongly influenced by post-consolidation processes. By contrast, recall performance was significantly different between all sessions except 24 hours and 1 week. Thus relatively rapid learning occurs initially and tapers off over time.

The relationship between working memory and recognition memory performance is interesting. Forward digit span, but not backward digit span, was significantly correlated with recognition immediately and at 24 hours at encoding. It is speculation, but the timing of the correlation may be indicative of specific common mechanisms, namely encoding and consolidation. The association between better digit span and better recognition could be due to either improved encoding or improved retrieval. Given that digit span does not correlate with recall, which is more demanding of retrieval processes, it is more likely that an encoding process underlies the relationship. Further, because there is an association at 24 hours, and because this time point is central to systems-level consolidation, it is also possible there is a common consolidation mechanism involved.

The relationship between order memory and recognition performance becomes decreasingly significant over time for recognition memory. However, the relationship becomes more significant over time for recall. Perhaps this is because as the

recognition task becomes more difficult over time, familiarity might make an increasingly larger contribution performance relative to recollection. One might expect order memory to be more related to recollection because both are more demanding on retrieval and explicit memory than familiarity is. Indeed, when we separated performance on the different multiple choice questions (which provide separate measures of recollection for items, associations, and item familiarity), accuracy on recollection questions deteriorates faster than accuracy for familiarity questions. As for the relationship between recall and order memory becoming more significant with time, this agrees with the above speculation. Recall is very demanding on explicit memory and would only become more so with time.

5.2 Between-Group Analyses: Genes, Sex, & Brain Structure

Regarding our three explicit hypotheses, we did not find what we set out to discover. Although we did find the expected allelic trend based on the literature for Kibra, ADCY8, and BDNF, we failed to find a temporal dissociation of Kibra and ADCY8's influence on memory as hypothesized. However, we suspect that we need more subjects in order to make a definitive statement that Kibra and ADCY8 do not affect memory in the way that we suggested. Our speculation is based on the fact that we found the expected trend between groups for overall performance on both recognition and recall, despite testing relatively few subjects in a genetic association study.

As for Kibra, we failed to replicate the robust effect found by Papassotiropoulos *et al.* In fact, Need *et al.* also failed to replicate the effect of Kibra on human memory with two large cohorts of European origin using multiple verbal memory tasks including the Auditory Verbal Learning Task, AVLT (Need 2007). They note "these results argue against a strong and general effect of Kibra on episodic memory and highlight the

critical need for large and consistently phenotyped cohorts to explore the relationship between genetic variation and human cognition" (Need 2007). Our lack of a significant finding may similarly indicate that Kibra does not influence episodic memory. However, given that we only had 18 subjects (compared with Papassotiropoulous *et al.* who had 200+ subjects) and that we found the expected trend nonetheless, we could interpret our findings equally as an indication of a real influence of this polymorphism on episodic memory performance.

Our finding with BDNF is more straightforward. Behaviourally, we found the expected trend but failed to reach significance. For recognition and recall, Met carriers had worse performance compared with Val homozygotes. Surprisingly the trend reversed for working memory. Met carriers performed better than Val homozygotes for both forward and backward digit span. The key finding was that VBM analysis with digit span and BDNF resulted in correlations that explain our behavioural data. Forward digit span and BDNF both significantly influence the same area in the parahippocampal gyrus, bilaterally. Forward digit span associates positively, and Met carriers have a larger relative grey matter volume in this area. This agrees with the behavioural finding that Met carriers have better working memory than Val homozygotes. Our results indicate that BDNF may influence working memory performance via structural changes in the parahippocampal gyrus. Given our findings with digit span and recognition memory described above, it is also possible that BDNF influences recognition performance through its influence on brain structure. This is speculation, but warrants future investigation.

However, our results are curious when compared with the literature. Several studies have used VBM and volumetric tracing to study associations between BDNF and brain volume (Pezewas *et al.* 2004, Bueller *et al.* 2006). They have related BDNF

with the hippocampus, but in the opposite direction to our finding. Namely, Met carriers are associated with relatively reduced hippocampal volume. Perhaps the discrepancy with our results is because we found a difference in the parahippocampus rather than the hippocampus proper. Moreover, our results show an association with working memory and not the other memory measures (i.e. recognition and recall) in our study. Again, this result agrees with our behavioural data because Met carriers performed less well in our other memory tasks.

Our association with gender also conflicts with much of the literature regarding gender performance and verbal memory (Lewin, Wolgers & Herlitz 2001). Most studies report that females perform better than males in tests of verbal memory while males tend to perform better in tests of spatial memory (Herlitz, Nilsson & Backman 1997). Still, we believe that the gender dissociation we found is not an artefact because males performed better than females on both measures of recognition, recall, and spatial memory. Possible reasons for the incongruity between the literature and our results could be rooted in the modality we had subjects encode the word pairs, and/or the way in which they were tested at retrieval. Although it was a verbal memory task, the encoding by picture-matching could tap more visuospatial processes than purely verbal processing, which could explain by males performed better. Further, females performed (although marginally) better on the modified word task which taps predominantly verbal processes. It should be noted that we had two thirds as many females as males and still found a trend for better performance in males.

Our findings with the sex hormones and memory performance provide possible insight into our gender dissociation results. It is known that sex hormones influence brain structure in humans (Pol 2006). For instance, in transsexual individuals undergoing hormonal therapy, anti-androgen + estrogen treatments induce a decrease in

adult brain volume (in male-to-female individuals) while androgen treatment (in female-to-male individuals) induces increased total brain and hypothalamic volume in adults (Pol 2006). Most studies that investigate the relationship between sex hormones and cognitive ability relate to studies of older individuals undergoing exogenous hormone therapy. Cherrier *et al.* exogenously manipulated serum levels of testosterone and found that decreased levels were associated with a decline in verbal but not spatial memory performance in healthy, young men (Cherrier *et al.* 2002) Bussiere *et al.* evaluated men undergoing androgen deprivation therapy (ADT) on a verbal memory task. They found that recognition performance fell from 2-minutes and onwards after encoding as compared with controls. Because androgen deprivation can decrease synaptic density in the hippocampus and memory in animals, there is evidence that androgen contributes to memory performance (Bussiere *et al.* 2005). More directed studies in animal models suggest a relationship between sex hormone levels and memory performance. Gonadectomized rats have decreased cognitive performance that can be restored with androgen replacement in several kinds of tasks (Frye *et al.* 2004, Ceccarelli & Scaramuzzino 2001). The mechanism by which sex hormones influence memory is unknown, but there is a clear association with performance.

However, upon closer comparison between gender and androgen associations with performance, the hypothesis that the sex hormone differences underlie the gender difference in performance becomes less tenable. Although the trends make sense for gender and androgen (that is, males and individuals with more testosterone perform better), the memory measures for which gender and androgen significantly influence are not the same. For instance, males significantly perform better than females on the spatial memory task while individuals with the short genotype perform worse (just). Despite our decision to investigate the androgen genotype being well justified by the

gender results, it is not clear how the two variables relate to each other in terms of memory mechanisms. Nevertheless, our results indicate the phenomena require further investigation.

5.3 Interindividual Differences: Metamemory

The certainty judgments we required subjects to make with respect to their answers in the recognition memory task positively related to accuracy. From the literature, it the direction of the relationship between certainty and accuracy depends primarily on the nature of the stimuli; there is no absolute relationship (Brewer & Sampaio 2006). According to Brewer & Sampaio, for non-deceptive items, it is a positive and reliable relationship, but for lists that mix non-deceptive with deceptive items, there may be no clear relationship, and for lists of deceptive items, there could be a negative relationship. Deceptive items refer to those that are highly similar to each other. We found a positive relationship but because it was not a perfect relationship, we could conclude that our items are a mixture of non-deceptive and deceptive items. In fact, we used repeated pictures (as foils) between pairs to be encoded that may have created deceptive items. Over time, the relationship between certainty and accuracy parallels the pattern in recognition performance. In other words, certainty was most predictive of accuracy during session three which was also when subjects performed the best in absolute scores of recognition memory. Certainty was least predictive of accuracy in the final session, also a time when performance on recognition memory was the worst.

Lastly, our self-rating questions provide another measure of metacognitive maturity in individuals and how this relates to memory behaviour. We asked subjects to evaluate how well they think they learn languages compared to others. Self-rating was significantly correlated with performance on almost all memory measures. One caveat

with this finding is that we asked subjects this question after they were tested in the final session, so perhaps they were really judging how well they thought they performed on the study overall, rather than answering the more general question. We should have asked subjects for a self-rating before they began the study to avoid all confounds. A further issue to consider is why self-ratings about memory did not correlate with memory performance, while self-ratings about language ability did.

Our follow-up questionnaire provides some insight into this conundrum. Correlation between self-ratings and objective memory measures indicates that self-rating is accurate for that measure. The self-ratings and objective measures are presumed to specifically tap into particular memory processes. When they correlate, this indicates a common memory mechanism is tapped from both angles. However, disagreement might indicate inaccuracy or insensitivity of the measures themselves. This is likely the case for our lack of correlation between some measures because none of our subjects are memory impaired relative to each other. For instance, recall and recognition performance correlated with none of the self-ratings. Because different underlying memory processes contribute to both recall and recognition performance, self-rating and objective measures will not likely map onto each other.

Likewise, subjective assessment of everyday memory proved not to be an indicative measure, possibly because it is designed to measure both retrieval and attentional tracking at once (Royle & Lincoln 2007). Assessment of both contentment and one's use of strategies is also complicated for this same reason. This is where our other memory measures are useful as they hone it on particular memory processes more directly. Prospective and short term memory both correlate with digit span, which is plausible since working memory relies on these processes. Performance on order memory correlates with retrospective, short and long term memory, and visual imagery

prowess. Use of visual imagery aids memory performance, thus it makes sense here. Finally, the modified word task (pattern separation) correlates with retrospective and short term memory. It is difficult to explain why retrospective and prospective memory dissociate between these measures, but this may be because these types of memory are not necessarily independent (Crawford *et al.* 2006).

We may speculate about plausible explanations for the correlations, but the greater challenge is to explain why there are not correlations where expected. For instance, why visual imagery associates with order memory but not digit span (especially backward) is puzzling. Similarly, why the modified word task associates with short term but not long term memory is perplexing, given that the task was performed 1 week after encoding. Overall, the follow-up questionnaire indicates that self-ratings about specific measures are useful in that they can provide insight into objective memory processes through their correlations. However, it also indicates that the design of such ratings must be deliberate in terms of which memory measures to which they are intended to map on.

6. Conclusions

Genetic associations with memory performance provide a way in which to bridge the gap of understanding between the cellular, neural, and psychological underpinnings of human memory. Furthermore, their involvement contributes to understanding the sources of natural variability in human memory performance. We fell short of characterizing the temporal profiles of influences on memory for our candidate genes. We also failed to reach significance for most memory measures. However, we had extremely few subjects for a genetic association study. Notwithstanding these shortcomings, our study demonstrates that this is a viable method for investigating variability in memory. Such studies may also have clinical relevance.

As Almedia *et al.* suggest, elucidating the long-term implications of a certain polymorphism that influences cognition could reveal genes which may confer greater risk of developing MCI or other cognitive problems (Almedia 2007). Overall, our study resulted in many trends between memory measures and genetic or structural traits that have laid a foundation for follow-up with larger numbers.

7. Appendixes

7.1 Follow-Up Online Metamemory Questionnaire:

(To assess Contentment; taken from Troyer & Rich 2002)

1. Please indicate how much you agree or disagree with the following statements:
1=Strongly Disagree, 2=Disagree, 3=Undecided, 4=Agree, 5=Strongly Agree

- I am generally pleased with my memory ability.
- There is something seriously wrong with my memory.
- If something is important, I will probably remember it.
- When I forget something, I fear that I may have a serious memory problem, like Alzheimer's disease.
- My memory is worse than most other people my age.
- I have confidence in my ability to remember things.
- I feel unhappy when I think about my memory ability.
- I worry that others will notice that my memory is not very good.
- When I have trouble remembering something, I'm not too hard on myself.
- I am concerned about my memory.
- My memory is really going downhill lately.
- I am generally satisfied with my memory ability.
- I don't get upset when I have trouble remembering something.
- I worry that I will forget something important.
- I am embarrassed about my memory ability.
- I get annoyed or irritated with myself when I am forgetful.
- My memory is good for my age.
- I worry about my memory ability.

(To assess Ability; taken from Troyer & Rich 2002)

2. Please indicate how frequently the following statements apply to you:
1=All the time, 2=Often, 3=Sometimes, 4=Rarely, 5=Never

- How often do you forget to pay a bill on time?
- How often do you misplace something you use daily, like your keys or glasses?
- How often do you have trouble remembering a telephone number you just looked up?
- How often do you not recall the name of someone you just met?
- How often do you leave something behind when you meant to bring it with you?
- How often do you forget an appointment?
- How often do you forget what you were just about to do; for example, walk into a room and forget what you went there to do?
- How often do you forget to run an errand?
- How often do you have difficulty coming up with a specific word that you want?

- How often do you have trouble remembering details from a newspaper or magazine article you read earlier that day?
- How often do you forget to take medication?
- How often do you not recall the name of someone you have known for some time?
- How often do you forget to pass on a message?
- How often do you forget what you were going to say in conversation?
- How often do you forget a birthday or anniversary that you used to know well?
- How often do you forget a telephone number you use frequently?
- How often do you retell a story or joke to the same person because you forgot that you had already told him or her?
- How often do you misplace something that you put away a few days ago?
- How often do you forget to buy something you intended to buy?
- How often do you forget details about a recent conversation?

(To assess Use of Strategies; taken from Troyer & Rich 2002)

3. Please indicate how often you use the following strategies:
1=All the time, 2=Often, 3=Sometimes, 4=Rarely, 5=Never

- How often do you use a timer or alarm to remind you when to do something?
- How often do you ask someone to help you remember something or to remind you to do something?
- How often do you create a rhyme out of what you want to remember?
- How often do you create a visual image of something you want to remember, like a name and a face?
- How often do you write things on a calendar, such as appointments or things you need to do?
- How often do you go through the alphabet one letter at a time to see if it sparks a memory for a name or word?
- How often do you organize information you want to remember; for example, organize your grocery list according
- to food groups?
- How often do you say something out loud in order to remember it, such as a telephone number you just looked up?
- How often do you use a routine to remember important things, like checking that you have your wallet and keys when you leave home?
- How often do you make a list, such as a grocery list or a list of things to do?
- How often do you mentally elaborate on something you want to remember; for example, focus on a lot of the details?
- How often do you put something in a prominent place to remind you to do something, like putting your umbrella by the front door so that you will remember to take it with you?
- How often do you repeat something to yourself at increasingly longer and longer intervals so that you will remember it?
- How often do you create a story to link together information you want to remember?
- How often do you write down in a notebook things that you want to remember?

- How often do you create an acronym out of the first letters in a list of things to remember, such as carrots, apples, and bread (cab) ?
- How often do you intentionally concentrate hard on something so that you will remember it?
- How often do you write a note or reminder for yourself (other than on a calendar or in a notebook)?
- How often do you mentally retrace your steps in order to remember something, such as the location of a misplaced item?

(To assess Prospective & Retrospective Memory; taken from Crawford *et al.* 2006)

4. Please indicate how frequently these statements apply to you:
1=Never, 2=Rarely, 3=Sometimes, 4=Quite Often, 5=Very Often

- Do you decide to do something in a few minutes time and then forget to do it?
- Do you fail to recognize a place you have visited before?
- Do you fail to do something you were supposed to do a few minutes later even though it is right there in front of you, like taking a pill or turning off the kettle?
- Do you forget something you were told a few minutes before?
- Do you forget appointments if you are not prompted by someone else or by a reminder such as a calendar or diary?
- Do you fail to recognize a character in a radio or television show from scene to scene?
- Do you forget to buy something you plan to buy, like a birthday card, even when you see it in the shop?
- Do you fail to recall things that have happened to you in the last few days?
- Do you repeated the same story to the same person on different occasions?
- Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it is right there in front of you?
- Do you mislay something that you have just put down, like a magazine or glasses?
- Do you fail to mention or give something to a visitor that you were asked to pass on?
- Do you look at something without realizing you have seen it moments before?
- If you tried to contact a friend or relative who was out, would you forget to try again later?
- Do you forget what you watched on television the previous day?
- Do you forget to tell someone something you had meant to mention a few minutes ago?

(To assess Everyday memory; taken from Royle & Lincoln 2007)

5. Please indicate how frequently these statements apply to you.
Once or less in the last month / More than once a month but less than once a week / About once a week / More than once a week or less than once a day / Once or more in a day

- Having to check whether you have done something that you should have done.
- Forgetting when it was that something happened; for example, whether it was yesterday or last week.

- Forgetting that you were told something yesterday or a few days ago, and maybe having to be reminded about it.
- Starting to read something (a book or an article in a newspaper, or a magazine) without realizing you have already read it before.
- Finding that a word is 'on the tip of your tongue'. You know what it is but cannot quite find it.
- Completely forgetting to do things you said you would do, and things you planned to do.
- Forgetting important details of what you did or what happened to you the day before.
- When talking to someone, forgetting what you have just said. Maybe saying 'what was I talking about?'
- When reading a newspaper or magazine, being unable to follow the thread of the story; losing track of what it is about.
- Forgetting to tell somebody something important, perhaps forgetting to pass on a message or remind someone of something.
- Getting the details of what someone told you mixed up and confused.
- Forgetting where things are normally kept or looking for them in the wrong place.
- Repeating to someone what you have just told them or asking someone the same question twice.

(To assess Visual Imagery; taken from the VVIQ, http://www.staff.city.ac.uk/d.marks/vviq.htm)

Visual imagery refers to the ability to visualize, that is, the ability to form mental pictures, or to "see in the mind's eye". Marked individual differences have been found in the strength and clarity of reported visual imagery. The aim of this test is to determine the vividness of your visual imagery. The items of the test will possibly bring certain images to your mind. You are asked to rate the vividness of each image by reference to the 5-point scale given below. Try to do each item separately, independent of how you may have done other items.
Complete the following 4 questions with your eyes OPEN.

6. In answering items 1 to 4, think of some relative or friend whom you frequently see (but who is not with you at present) and consider carefully the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- The exact contour of face, head, shoulders and body.
- Characteristic poses of head, attitudes of body etc.
- The precise carriage, length of step, etc. in walking.
- The different colours worn in some familiar clothes.

7. Visualise the rising sun. Consider carefully the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- The sun is rising above the horizon into a hazy sky
- The sky clears and surrounds the sun with blueness Clouds.
- A storm blows up, with flashes of lightening
- A rainbow appears

8. Think of the front of a shop which you often go to. Consider the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- The overall appearance of the shop from the opposite side of the road
- A window display including colours, shape and details of individual items for sale.
- You are near the entrance. The colour, shape and details of the door.
- You enter the shop and go to the counter. The counter assistant serves you. Money changes hands.

9. Finally, think of a country scene which involves trees, mountains an a lake. Consider the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- The contours of the landscape
- The colour and shape of the trees
- The colour and shape of the lake
- A strong wind blows on the tree and on the lake causing waves

You will now be asked the same four questions you just completed, but this time, answer with your eyes CLOSED. Try and give your "eyes closed" rating independently of the "eyes open" rating. The two ratings for a given item may not in all cases be the same.

10. In answering items 1 to 4, think of some relative or friend whom you frequently see (but who is not with you at present) and consider carefully the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- Characteristic poses of head, attitudes of body etc.
- The precise carriage, length of step, etc. in walking.
- The different colours worn in some familiar clothes.

11. Visualise the rising sun. Consider carefully the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- The sun is rising above the horizon into a hazy sky
- The sky clears and surrounds the sun with blueness Clouds.
- A storm blows up, with flashes of lightening
- A rainbow appears

12. Think of the front of a shop which you often go to. Consider the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- The overall appearance of the shop from the opposite side of the road
- A window display including colours, shape and details of individual items for sale.
- You are near the entrance. The colour, shape and details of the door.
- You enter the shop and go to the counter. The counter assistant serves you.
- Money changes hands.

13. Finally, think of a country scene which involves trees, mountains an a lake. Consider the picture that comes before your mind's eye.
Perfectly clear and as vivid as normal vision / Clear and reasonably vivid / Moderately clear and vivid / Vague and dim / No image at all, you only "know" that you are thinking of an object

- The contours of the landscape
- The colour and shape of the trees
- The colour and shape of the lake
- A strong wind blows on the tree and on the lake causing waves

(To assess the use of strategies; compiled by ourselves)

14. Please rate how often you use the following strategies (for example, when studying for a test, exam, or any other time when you must learn information):
Never, because I know it doesn't work for me /Never / Rarely / Sometimes / Often / Always /Always, because I know it works best

- I write the information out in order to learn it
- I form visual images and associations in my mind
- I read or say the information out loud to myself
- I discuss the new material with others
- I form anagrams, rhymes, or stories about the new material
- I memorize where on the page(s) the information is written
- I highlight/underline/circle key words in different colours
- I quiz myself on the new material using cue-cards or other methods

15. Please rate how often you use the following strategies (for example, when studying for a test, exam, or any other time when you must learn information):
Never, because I know it doesn't work for me / Never / Rarely / Sometimes / Often / Always /Always, because I know it works best

- I repeat material over and over, one at a time
- I repeat material over and over, in a cumulative fashion, rehearsing old items along with new items
- I look for meaningful, semantic relationships among items I must learn
- I study information in order of importance, studying the most important first
- I expend more effort to study the material that is not yet learned

(To assess foreign language learning ability; compiled by ourselves)

16. Finally, please answer the following questions about your ability to learn new languages. Rate your own ability as compared with others on a 1-5 scale:
1=Very Poor 2=Poor 3=Average 4=Good 5=Excellent

- How would you rate your ability to learn another language as compared with others?
- When learning another language, how well do you think you learn new vocabulary?
- When learning another language, how well do you think you pick up new accents?
- When learning another language, how well do you think you learn new grammar rules and structure?
- How well do you think you learned the Swahili words in our study?

7.2 English-Swahili Word Pairs:

- Nelson & Dunlosky Word List:

Mbwa	-	dog	pazia	-	curtain
Lulu	-	pearl	theluji	-	snow
Wingu	-	cloud	tumbili	-	monkey
Iktisadi	-	economy	vuke	-	steam
Goti	-	knee	wasaa	-	leisure
Yai	-	egg	kaburi	-	grave
Pombe	-	beer	rafiki	-	friend
Godoro	-	mattress	sala	-	prayer
Fagio	-	broom	kauptula	-	shorts
Tabibu	-	doctor	mashua	-	boat
Buu	-	maggot	punda	-	donkey
Ndoo	-	bucket	usingizi	-	sleep
Nyanya	-	tomato	ziwa	-	lake
Sumu	-	poison	elimu	-	science
Roho	-	soul	zeituni	-	olives
Chakula	-	food	adhama	-	honor
Kaa	-	crab	adui	-	enemy
Maiti	-	corpse	bustani	-	garden
Farasi	-	horse	dafina	-	treasure
Leso	-	scarf	embe	-	mango
Hariri	-	silk	nabii	-	property
Malkia	-	queen	pafu	-	lung
Rembo	-	ornament	pamba	-	cotton
Zulia	-	carpet	samadi	-	manure
Pipa	-	barrel	baharia	-	sailor
Fununu	-	rumor	chama	-	society

Jani	-	leaf	chura	-	frog
Lozi	-	almond	nira	-	yoke
Wakili	-	agent	yatima	-	orphan
Bahasha	-	envelope	chaza	-	oyster
Fumbo	-	mystery	hamira	-	yeast
Vumbi	-	dust	ambo	-	glue
Banadri	-	harbour	dalasini	-	cinnamon
Inda	-	spite	jeraha	-	wound
Lango	-	gate	nanga	-	anchor
Paji	-	forehead	zabibu	-	grapes
Desturi	-	custom	duara	-	wheel
Handaki	-	trench	joko	-	kiln
Mfupa	-	bone	sahani	-	plate
Sanda	-	shroud	utenzi	-	poem
Adha	-	trouble	jibini	-	cheese
Kasuku	-	parrot	rushwa	-	bribe
Tajiri	-	merchant	talaka	-	divorce
Yamini	-	oath	ankra	-	invoice
Chimbo	-	quarry	gharika	-	flood
Gutu	-	stump	hadithi	-	story
Kamba	-	rope	lawama	-	blame
Nafaka	-	corn	fahali	-	bull
Mshoni	-	tailor	ruba	-	leach
Ladha	-	flavour	ubini	-	forgery

All words have greater than 3 characters; all are nouns; none are hyphenated, compound words, or cognates. Nelson & Dunlosky (1994) compiled their words from *Swahili-English Dictionary* (Perrott 1965). Subjects encoded these words in the fMRI scanner at 24 hours after encoding (data not analyzed in this thesis).

- British Picture Vocabulary Scale: English words for pictures were translated into Swahili using http://kamusiproject.org/. We generated 144 pairs.

chapuo	drum	inzi	housefly
ngombe	cow	uchumaji	picking
afa	accident	jabali	rock
chakua	dentist	nunua	shopping
kabidhi	delivering	mangaja	bells
mtoriro	vegetable	bunge	parliament
mkalimu	teacher	nishani	badge
kilimbili	wrist	hema	tent
amkio	greeting	jarida	magazine
roshani	balcony	tadubiri	repair
jitokeza	emerging	gofu	wreck
kishiku	wedge	kipimajoto	thermostat
mnajimu	archaeologist	para	cake
wonyesho	exhibition	gogo	trunk
mnara	beacon	maraba	cubic
njiti	wooden	heleni	earring
kipenyo	socket	ndevu	beard
ukomba	talon	ngota	peck
hewa	emission	lambo	dam
defa	time	gebali	cliff
kosi	neck	dirisha	square
kipapatiko	feather	jini	fairy
gondi	claw	fanusi	lantern
msitu	forest	buruma	pipe
chupa	flask	bandika	pasting
tunda	fruit	cheuzi	pair
boi	waiter	rembo	ornament
dege	fern	gwafua	snarling
mimba	seed	thelatha	triplet
bwawa	swamp	kisua	garment
chora	engraving	ondoka	departing
kifano	parallel	gari	car
fumbata	embracing	chombo	furniture
msambamba	parallelogram	abedari	pulley
memeteka	furious	matumizi	consuming
dudumi	antler	mshale	arrow

nyenyeleza	confiding	kiwiko	ankle
tembezi	ambulation	pingo	bolt
daraja	ladder	upakio	plastering
mshumaa	candle	akali	isolation
popotoa	spanner	mzunguko	orbit
kituko	horror	kiunzi	easel
tai	eagle	angavu	transparent
anisi	delighted	sanamu	camera
chiririka	dripping	mwanzi	nostril
butaa	surprise	saidiwa	assisting
mwonyeshaji	entertainer	shangilia	applauding
bori	tusk	mata	archery
nyoka	snake	peketeka	perforated
tema	chopping	kilimo	agriculture
nanga	anchor	ndoo	bucket
chuja	sorting	kakawana	athlete
kiungo	link	kubaza	inflated
uwanja	stadium	chanjo	inoculation
rekebishika	adjustable	faranga	penguin
ihramu	pyramid	nyuki	bee
bahasha	envelope	gawa	sharing
ogofyo	dangerous	manyoya	furry
dafrao	collision	sufi	woolly
chavu	net	tishali	tugging
kimiminiko	liquid	chokochoko	disagreement
chanzo	root	bizari	grain
neli	tubular	vuke	steam
kinagiri	locket	chororo	weasel
bufuu	scalp	msasi	hunter
dumaa	stunt	umbo	silhouette
balia	catastrophe	darasa	lecturing
upeo	summit	kaule	porcelain
pete	circle	mpira	ball
msanifu	artist	taabani	weary
kifaa	utensil	kidoto	goblet
siraji	torch	dari	roof

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